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Syntheses and Reactions of 3-Amino-4(3H)-pyrimidones[1]

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The reaction of β-keto esters with aminoguanidine afforded 2,3-diamino-4(3H)-pyrimidones (IV), which were employed for the cyclization to 5,8-dihydro-*s*-triazolo [1,5-*a*]pyrimidin-5-ones (V) and 1,2-dihydro-3-methyl-6H-pyrimido[1,2-*b*]*as*-triazine-2,6-diones (VIII).

Further treatment of β-keto esters with thiosemicarbazide gave 3-amino-4(3H)-oxo-2(1H)-pyrimidinethiones (XII). 7-Methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (XIV) was derived from the 6-methyl derivative of XII.

Two N-aminopyrimidines, *i.e.*, 1,4,6-triamino-[3] and 6-amino-1-dimethylamino-4(3H)-oxo-2(1H)-pyrimidinethiones[4] have been prepared, but no report concerned the utility of these compounds for the condensed ring system synthesis. Meanwhile, the condensation of aminoguanidine (I) or thiosemicarbazide (II) with ethyl acetoacetate in aqueous medium has been reported to give 3-methyl-5-pyrazolone derivatives.[5] In a reinvestigation of this reaction in the presence of sodium ethoxide, we observed quite different results. This paper describes the synthesis of N-aminopyrimidones from the reaction of I or II with β-keto esters (IIIa—c), and the condensed ring system syntheses using N-aminopyrimidones.

A solution of equimolecular amounts (0.02 moles) of I and III in ethanol containing 0.01 mole of sodium ethoxide was refluxed to give a series of 2,3-diamino-4(3H)-pyrimidones (IV).

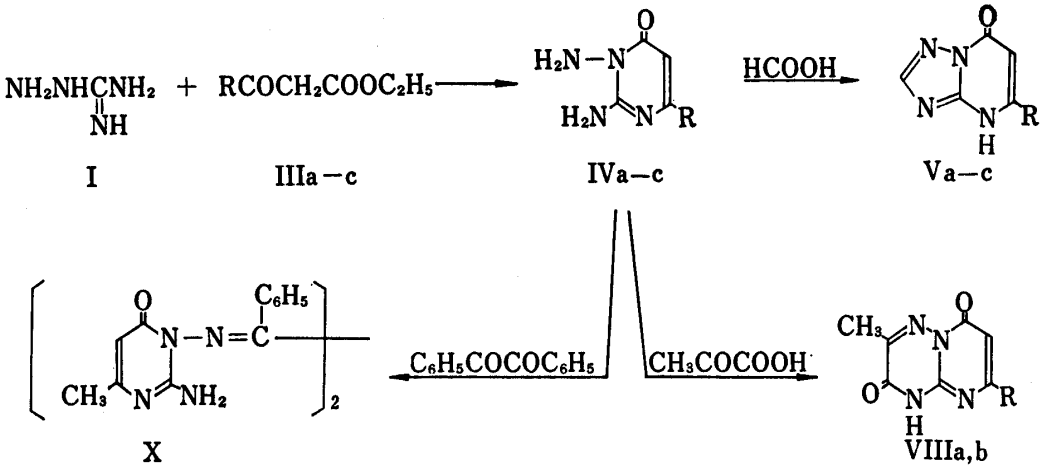
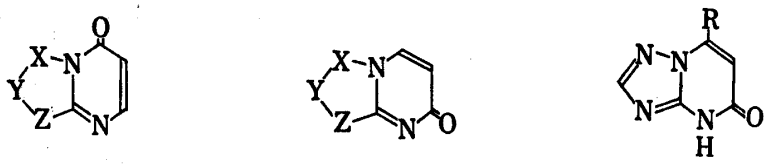


Chart 1

1) This work was presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July, 1970.
2) Location: *Mejiro-dai, Bunkyo-ku, Tokyo.*
3) E.C. Taylor and R.W. Morrison, *J. Org. Chem.*, 32, 2379 (1967).
4) E. Carstens, H.G. Kazmirowski, and J. Donat, East German Patent, 23546 (1963).
5) *a*) P. Shestakov and N. Kazakov, *J. Russ. Phys. Chem. Soc.*, 44, 1318 (1912) [*C. A.*, 7, 984 (1913)]; *b*) S.C.De, *Quart. J. Indian Chem. Soc.*, 3, 33 (1926) [*C. A.*, 21, 2128 (1927)].

Products IV were confirmed their structures by the similarities of ultraviolet (UV) spectra with spectra of the corresponding isocytosines and by the following reaction. Reflux of IV with formic acid for 8 hr afforded 4H-7-oxo-*s*-triazolo[1,5-*a*]pyrimidines (V). 5-Methyl derivative (Vb) was identical with the authentic sample[6] and infrared (IR) spectra of V showed the carbonyl absorption at 1705—1710 cm^{-1}. Allen, *et al.*[7] reported on the IR spectroscopy of 4- and 6-oxo-polyazaindenes (VIa and VIb) that the 4-one series, VIa, showed the amide carbonyl band below 6 μ, whereas the 6-one series, VIb, showed a band at 6 μ. Therefore, the observed carbonyl band might support the structure of V, but not the alternative (VII). Compounds IV and V obtained hereof are listed in Table I and II.



VIa VIb VII

Chart 2

Table I. 3-Amino-4(3H)-pyrimidone Derivatives (IV, V, VIII, XII, XIII)

Compd. No.	Yield (%)	Recryst. solvent	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa	17	EtOH	178—180	$C_4H_6ON_4$	38.09	4.80	44.43	38.29	4.62	44.21
IVb	64	EtOH	283	$C_5H_8ON_4$	42.85	5.75	39.98	42.97	5.66	39.95
IVc	32	dil. EtOH	233—234.5	$C_{10}H_{10}ON_4$	59.39	4.98	27.71	59.49	5.12	28.08
Va	45	H_2O	275—276	$C_5H_4ON_4$	44.12	2.96	41.17	44.00	3.11	41.35
Vb	80	H_2O	278[a]	$C_6H_6ON_4$	48.00	4.03	37.32	48.25	4.00	37.51
Vc	62	DMF–EtOH	277.5—278.5	$C_{11}H_8ON_4$	62.25	3.80	26.40	62.53	3.76	—
VIIIa	89	dil. EtOH	282	$C_7H_6O_2N_4$	47.19	3.39	31.45	47.22	3.46	31.32
VIIIb	93	H_2O	300	$C_8H_8O_2N_4$	49.99	4.20	29.16	49.91	4.17	29.35
XIIa	18	H_2O	217—218	$C_4H_5ON_3S$	33.57	3.52	29.37	33.76	3.47	29.53
XIIb	25	H_2O	236.5—237.5	$C_5H_7ON_3S$[b]	38.22	4.49	26.74	38.20	4.63	26.51
XIIIa	75	EtOH	196—198	$C_5H_5O_2N_3S$	35.09	2.95	24.56	35.04	3.05	24.70
XIIIb	82	dil. EtOH	219—220	$C_6H_7O_2N_3S$[c]	38.92	3.81	22.70	38.90	3.96	23.12

a) lit.[8] mp 278° *b*) Mass Spectrum *m/e*: 157 (M^+) *c*) Mass Spectrum *m/e*: 185 (M^+)

Further cyclization study revealed that IV, upon treatment with pyruvic acid, could be converted into 1,2-dihydro-3-methyl-6H-pyrimido[1,2-*b*]as-triazine-2,6-diones (VIII). The pyrimido[1,2-*b*]*as*-triazines are examples of a new heterocyclic ring system. IR spectra of VIII were characteristic to have two amide carbonyl bands at 1710 and 1675 cm^{-1}.

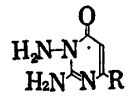
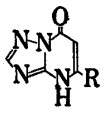
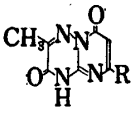
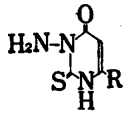
Treatment of IVb (IV, R=Me) with benzil gave the compound (X), $C_{24}H_{22}O_2N_8$, corresponding to the condensation product of IVb with benzil in a mole ratio of 2:1. Its IR spectrum showed the amino band at 3300 cm^{-1} and the carbonyl band at 1705 cm^{-1}. Any amount of the expected pyrimido[1,2-*b*]*as*-triazine compound was not detected in the reaction mixture.

In the structure of IV, the 3-amino group was considered as a group existing in the hydrazine moiety, while the 2-amino group as that in the guanidine moiety. Therefore, the 3-amino group might have the enhanced reactivity to condense with the keto group of pyruvic

6) C. Bülow, *Chem. Ber.*, **42**, 4642 (1909); C.F.H. Allen, H.R. Beilfuss, D.M. Burness, G.A. Reynolds, J.F. Tinker, and J.A. vanAllan, *J. Org. Chem.*, **24**, 787 (1959).

7) C.F.H. Allen, H.R. Beilfus, D.M. Burness, G.A. Reynolds, J.F. Tinkee, and J.A. van Allan, *J. Org. Chem.*, **24**, 779 (1959).

Table II. Spectral Data of 3-Amino-4(3H)-pyrimidone Derivatives

Compound	No.	R	IR ν_{max}^{KBr} cm^{-1} NH$_2$	IR ν_{max}^{KBr} cm^{-1} C=O	UV λ_{max} mμ (log ε)	
	IVa	H	3330	1685	214 (4.7059) 257 (4.5410)	pH 1
	IVb	CH_3	3320	1680	219 (4.8325) 258 (4.7204)	pH 1
	IVc	C_6H_5	3320	1685	285 (4.4786)	pH 1
	Va	H		1705	211 (3.5502) 243 (3.5592) 277 (3.7243)	MeOH
	Vb	CH_3		1710	214 (3.6284) 245 (3.5670) 273 (3.7818)	MeOH
	Vc	C_6H_5		1705	210 (4.1931) 245 (4.4281) 307 (4.8451)	MeOH
	VIIIa	H		1670 1710	230 (4.3284) 253 (4.2989) 294 (4.1038)	MeOH
	VIIIb	CH_3		1670 1715	211 (4.1297) 234 (4.134) 251.5 (4.1309) 295 (3.7762)	MeOH
	XIIa	H	3340	1675	236 (4.3766) 275 (4.4800)	pH 1
	XIIb	CH_3	3280	1675	235 (3.9004) 279 (4.2041)	pH 1

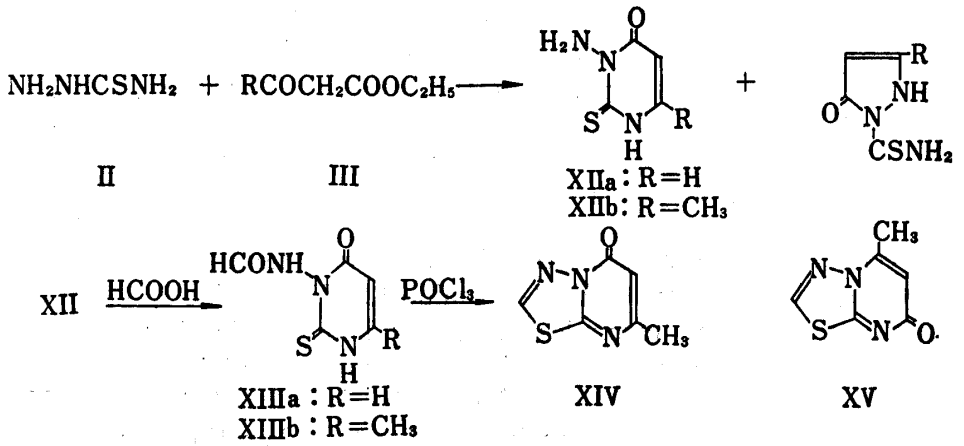


Chart 3

acid or benzil resulting the formation of VIII or X. Accordingly, the structures IX and XI wich are shown in Chart 1 instead of VIII and X, respectively, were excluded.

Next, condensation of II with III in the presence of two equivalent amount of sodium ethoxide gave 3-amino-4(3H)-oxo-2(1H)-pyrimidinethiones(XII) with the formation of 5-pyrazolone derivatives.[5] The UV spectra of XII were similar with those of the corresponding 2-thiouracils. Further evidence to support the structure of XII was obtained by the following reactions. Reflux of XII with formic acid afforded N-formyl derivatives (XIII). Subsequent treatment of the 6-methyl compound (XIIIb) with phosphorus oxychloride led to

yield 7-methyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one(XIV). These reactions are shown in Chart 3. Compound XIV did not form a sodium salt and its UV spectrum was similar with the spectrum of 2-ethyl derivative[7] of XIV. The IR spectrum (KBr) of XIV showed the amide carbonyl band at 1710 cm^{-1}, which was consistent with the proposed structure of XIV having a polyazaindene-4-one structure, VIa. but not with an alternative structure (XV) having a polyazaindene-6-one structure, VIb.

Additional method to distinguish two series of 4- and 6-oxo-polyazaindenes, VIa and VIb, was further reported by Allen, *et al.*[7] from the comparison of the intensity of the absorption peak in the c region (300—400 mμ) with that of the band in the b region (250—270 mμ). They found that in the VIa (4-one) series, the ratio of the extinction coefficient of the c to that of the b band was always greater than 1, whereas in the VIb (6-one) series the c band was at best only one third the intensity of the b band. The intensity ratio of c/b was found to be 1.77 from the spectrum of XIV [λ_{max}^{MeOH} mμ (ε); 219 (8100), 231 (6850), 253 (5310), and 305(9400)]. This figure might also support that XIV was the compound possessing the VIa structure.

Compounds VIII, XII and XIII obtained thereof are listed in Table I and II.

Experimental[8]

General Procedure for Synthesis of 2,3-Diamino-4(3H)-pyrimidones (IV)——To a solution of EtONa prepared from 0.23 g of Na and 25 ml of anhyd. EtOH was added 2.21 g of aminoguanidine hydrochloride and the whole was warmed on a water bath for 15 min. After removal of the deposited NaCl by filtration, 0.02 mole of β-keto ester was added into the filtrate, and the mixture was refluxed for 3—5 hr. After cooling, the precipitates were collected and recrystallized to give IV as colorless needles.

General Procedure for Synthesis of 5,8-dihydro-*s*-triazolo[1,5-*a*]pyrimidin-5-ones (V)——A solution of 0.002 mole of IV in 6 ml of formic acid was refluxed for 8 hr. After removal of an excess amount of formic acid, the resulted precipitates were collected and recrystallized to give colorless needles of V.

General Procedure for Synthesis of 1,2-Dihydro-3-methyl-6H-pyrimido[1,2-*b*]*as*-triazin-2,6-diones (VIII)——A solution of 0.0025 mole of IV and 640 mg of pyruvic acid in 10 ml of 70% EtOH was refluxed on a water bath for 1 hr. Recrystallization of the precipitates from EtOH yielded VIII as colorless needles.

Condensation of IVb with Benzil——A mixture of 200 mg of IVb and 300 mg of benzil was heated at 230—240° for 10 min. After cooling, the solidified product was recrystallized from EtOH to form yellow fine needles, mp 228—229°. Yield, 240 mg (84%). Product X was insoluble in aq. NaOH. *Anal.* Calcd. for $C_{24}H_{22}O_2N_8$: C, 63.42; H, 4.85; N, 24.66. Found: C, 63.31; H, 4.83; N, 24.61. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH_2), 1705 (C=O).

General Procedure for Synthesis of 3-Amino-4(3H)-oxo-2(1H)-pyrimidinethiones (XII)——To a solution of EtONa prepared from 4.6 g of Na and 100 ml of anhyd. EtOH were added 9.1 g of fine powdered thiosemicarbazide and 0.1 mole of β-keto ester and the whole was refluxed for 4 hr. The precipitates were collected, dissolved in water and acidified with AcOH. The resulted precipitates were collected and extracted four times with hot water. The extracts were combined, cooled to yield XII as the precipitates. Recrystallization of XII gave colorless needles.

A hot water insoluble substance was recrystallized from EtOH to give the pyrazolone compound, whose mp, IR and UV spectra were identical with the authentic sample of the corresponding 5-pyrazolone derivative.[5b]

General Procedure for Synthesis of 3-Formamido-4(3H)-oxo-2(1H)-pyrimidinethiones (XIII)——A solution of 500 mg of XII in 5 ml of formic acid was refluxed for 3 hr. Precipitates were collected and recrystallized to form colorless needles.

7-Methyl-5H-1,3,4-thiadiazolo[3,2-α]pyrimidin-5-one (XIV)——A suspension of 185 mg of XIIIb in 1 ml of $POCl_3$ was refluxed gently for 30 min until the whole became a clear solution. After removal of an excess amount of $POCl_3$ under diminished pressure, the residue was poured into an ice-water. The resulted solution was evaporated *in vacuo*, and then MeOH was added into the residual oil for crystallization. The solidified product was collected and recrystallized from dil. EtOH to yield 110 mg (66%) of colorless needles, mp 158—160°. *Anal.* Calcd. for $C_6H_5ON_3S$: C, 43.12; H, 3.02; N, 25.15. Found: C, 42.90; H, 3.02; N, 25.38. Mass Spectrum *m/e*: 167 (M^+). IR and UV spectral data are given in the text.

8) All melting points were uncorrected.