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A NOVEL ONE-STEP SYNTHESIS OF PYRIMIDINES AND CONDENSED PYRIMIDINES

Katsura Morita, Shigeru Kobayashi, Hiroshi Shimadzu and Michihiko Ochiai
Research and Development Division, Takeda Chemical Industries, Ltd.,
Juso, Osaka, Japan

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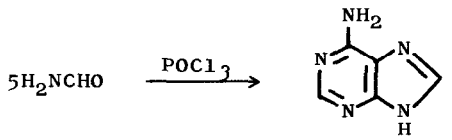
Previously, we reported a facile one-step synthesis of adenine in which adenine was obtained in 40-50% yields by heating a mixture of formamide and phosphorus oxychloride (1:2 mole ratio) in a sealed vessel (1). Theoretically, 1 mole of adenine is synthesized from 5 moles of formamide (eq.-1). As to the



(eq.-1)

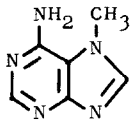
(I)

mechanism of this one-step synthesis we have proposed a novel cyclization mechanism, which involves formation of a Vilsmeier-type reagent and subsequent cyclization of a pentamer to give adenine. A number of N-substituted adenines have recently been discovered widely in nature, some of which are receiving attention from the point of view of interesting biological activities.

In the hope of extending the synthesis of adenine we attempted to treat a mixture of formamide and N-methylformamide in the presence of phosphorus oxychloride to see if N-methyladenine could be obtained. This brought us to the finding of the present single-step synthesis of pyrimidines and condensed pyrimidine heterocycles including N^7-methyladenine etc.

When a mixture of N-methylformamide, formamide, and phosphorus oxychloride was heated at 120° in a sealed vessel for 12 hours, there was obtained a UV-absorbing substance, which was separated from adenine by chromatography on silica gel using $CHCl_3$-methanol (3:2) as solvent, crystallized from water and

identified as N^7-methyladenine (eq.-2). Physical characteristics of this substance are summarized in Table I, which also includes UV-spectral data and pKa values of the known N-methyladenines for comparison.

$$H_3CNHCHO + 4H_2NCHO \xrightarrow[5\%]{POCl_3}$$  (eq.-2)

(II)

Table I. UV-Spectral Data and pKa Values of N-Methyladenines

	pH	λ max (mμ)	ε (x 10^4)	ε280/ε260	Isosbestic point (mμ)	pKa (50% DMF)
(II)	1.20	273.5	1.63	1.12	222, 236, 250	3.6
	11.95	270.5	1.25	0.80		
1-Methyl-adenine*1	4	259	1.17	0.23		
	13	270	1.44	0.85		
3-Methyl-adenine*2	H^+	274	1.59	1.26	240, 281	5.3
	OH^-	272	1.36	1.46		
7-Methyl-adenine*2	H^+	272	1.38	1.02	221, 232, 251	3.5
	OH^-	270	1.05	0.87		
9-Methyl-adenine*3	0.05N-HCl	260	1.55			
	0.05N-NaOH	260	1.55			

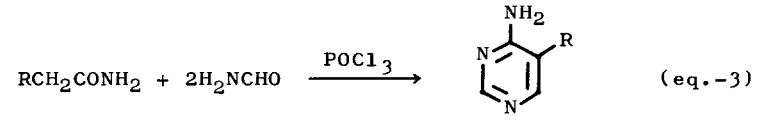
*1 J. Chem. Soc., 1960, 539.

*2 Compt. Rend., 253, 2994 (1961).

*3 J. Chem. Soc., 1937, 1912.

When acetamide was used in place of N-methylformamide in the aforementioned reaction we obtained 4-aminopyrimidine, whose IR spectrum was in complete accord with that of an authentic sample. The optimum conditions for the formation of 4-aminopyrimidine are described below: A mixture of acetamide, formamide and $POCl_3$ (1:2:3 mole ratio) was heated at 120° in a sealed vessel for 15 hr. The reaction mixture was diluted with water and the resulting solution was neutralized with sodium hydroxide and extracted with ethyl acetate. The extract was evaporated under reduced pressure and yielded a brown residue. Chromatography of this residue on silica gel using $CHCl_3$-acetone-methanol (70:30:5) as solvent yielded 4-aminopyrimidine as colorless crystals.

Similarly, propionamide and butyramide afford 4-amino-5-methylpyrimidine and 4-amino-5-ethylpyrimidine, respectively. These reactions furnish a convenient one-step synthesis of 4-amino-5-alkylpyrimidines as illustrated by the general equation (eq.-3). The compounds obtained by this novel one-step synthesis are summarized in Table II.



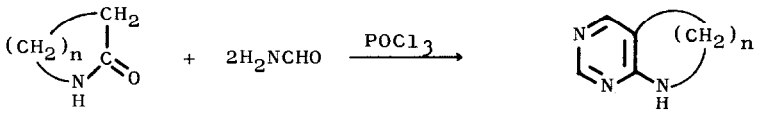
(eq.-3)

Table II. 4-Amino-5-alkylpyrimidines

R	m.p. (°C)	Lit. m.p.	Yield (%)
H-	149 - 151	151	32
CH_3-	170 - 173	176	28
CH_3CH_2-	160 - 162	163	16
$CH_3CH_2CH_2$-	162	*	24
$CH_3(CH_2)_2CH_2$-	103 - 105	*	17
$CH_3(CH_2)_4CH_2$-	119	*	18
$CH_3(CH_2)_6CH_2$-	125 - 126	*	16
$CH_3(CH_2)_{12}CH_2$-	118 - 119	*	27
$CH_3(CH_2)_{14}CH_2$-	113 - 114	*	21

* New compound.

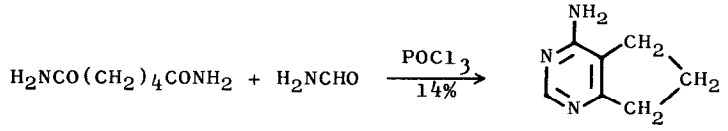
When α-pyrrolidone (III), δ-valerolactam (IV) and ε-caprolactam (V) were used as starting materials, there were obtained 5,6-dihydro-7H-pyrrolo[2,3-d] pyrimidine (VI), $C_6H_7N_3$, m.p. 113-114°, UV $\lambda_{max}^{H_2O}$ (pH 1) mμ (ε): 266 (10700), $\lambda_{max}^{H_2O}$ (pH 11) mμ (ε): 250, 284 (7560, 4180), 5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine (VII), $C_7H_9N_3$, m.p. 106-108°, UV $\lambda_{max}^{H_2O}$ (pH 1) mμ (ε): 262 (12100), $\lambda_{max}^{H_2O}$ (pH 11) mμ (ε): 247, 286 (9730, 4750), and 5,6,7,8-tetrahydro-9H-pyrimido [4,5-b]azepine (VIII), $C_8H_{11}N_3$ (M^+ at m/e 149) m.p. 99.5-100°, UV $\lambda_{max}^{H_2O}$ (pH 1) mμ (ε): 274 (11500), $\lambda_{max}^{H_2O}$ (pH 11) mμ (ε): 251, 282 (7640, 5210), respectively.



(III) n=2; (IV) n=3; (V) n=4

(VI) n=2 (9%); (VII) n=3 (15%); (VIII) n=4 (7%)

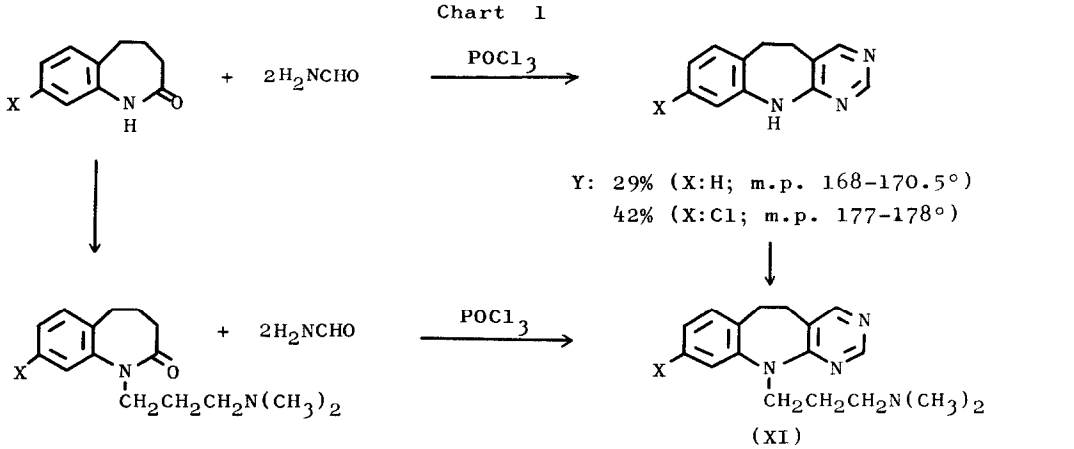
Interestingly, when adipamide (IX) was treated with phosphorus oxychloride under the conditions described above, 4-amino-6,7-dihydro-5H-cyclopenta[d] pyrimidine (X) was obtained. The identification of X was established by comparison of the UV spectral data (2).



(IX) (X) (eq.-4)

A hitherto unknown diazaisolog (XI) of the antidepressant drug, 5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[b,f]azepine (3), was also prepared by means of this novel one-step synthesis as shown in Chart 1.

Chart 1



Y: 29% (X:H; m.p. 168-170.5°)
42% (X:Cl; m.p. 177-178°)

(XI)

Y: 5% (X:H; m.p. 233-234° 2HCl salt)
18% (X:Cl; m.p. 91-92°)

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