[Chem. Pharm. Bull. 26(8)2497—2501(1978)]

UDC 547.853.3.04 : 547.298.1.04

The Synthesis and Reactions of Some Isoxazolo[3,4-*d*]pyrimidines

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(Received February 24, 1978)

The reaction of 6-hydroxyamino-1,3-dimethyluracil (**1**) with Vilsmeier reagent (phosphorus oxychloride and dimethylformamide) or arylaldehydes afforded 5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5H, 7H)-dione (**2**) and its 3-aryl derivatives (**10**—**17**), respectively. The 3-arylisoxazolo[3,4-*d*]pyrimidines (**9**, **10**) underwent photorearrangement to yield the corresponding 2-aryloxazolo[4,5-*d*]pyrimidines (**19**—**20**). Some reactions on **2** are also reported.

Keywords——6-hydroxyamino-1,3-dimethyluracil; Vilsmeier reagent; 5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5H, 7H)-dione; arylaldehyde; 3-aryl-5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5H, 7H)-diones; photorearrangement; 2-aryl-4,6-dimethyloxazolo[4,5-*d*]pyrimidine-5,7(4H, 6H)-diones

Isoxazolo[3,4-*d*]pyrimidines may be of biological interest since they can be considered analogs of purines by virtue of the 3,4-*d* fusion of the five membered ring to the pyrimidine nucleus. However, the literature survey revealed only three patented references[2)] for the construction of this heterocycle. We now report the synthesis and reactions of some isoxazolo-[3,4-*d*]pyrimidines.

Heating of 6-hydroxyamino-1,3-dimethyluracil (**1**)[3)] with a mixture of phosphorus oxychloride and dimethylformamide (Vilsmeier reagent) at 95° for 1 hr gave the expected 5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5H, 7H)-dione (**2**)[4)] in 59% yield. The structure of **2** was readily established by its elemental analysis and spectral data. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) revealed three singlets at δ 3.40 (N–Me), 3.54 (N–Me), and 10.00 (C^3–H), and the mass spectrum showed a strong parent ion at *m/e* 181.

The compound **2** was stable against acid hydrolysis. Namely, heating of **2** with 10% hydrochloric acid at 95° for 5 hr did not give any hydrolyzed product and the starting material was recovered. On the contrary, refluxing of **2** with ethanol containing piperidine for 1 hr resulted in cleavage of the isoxazole ring to give ethyl 6-amino-1,3-dimethyluracil-5-carboxylate (**3**)[5)] in a good yield.

The reaction of **2** with ammonium acetate in a mixture of sulfolane and acetic acid at 170° for 7 hr gave 1,3,7,9-tetramethylpyrido[2,3-*d*, 6,5-*d'*]dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetrone (**5**)[6)] in 7% yield as an only isolated product, and attempts to synthesize the tricycloquinazoline analog (**6**) having 1,3-dimethyluracils were unsuccessful.[7)] The formation of **5** presumably involves the hydrolytic N(1)–O(2) bond fission of **2** to 6-amino-5-formyl-1,3-dimethyluracil (**4**),[8)] followed by condensation with the another molecule of **4** accompanying

1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan*; *a*) To whom inquires should be addressed.
2) D.H. Kim and A.A. Santilli, U.S. Patent 3517008 [*C.A.*, **73**, 45545*e* (1970)]; L.K. Gibbons and A.A. Ramsey, German Patent, 2249162 [*C.A.*, **79**, 18763*s* (1973)]; L.K. Gibbons, German Patent, 2249163 [*C.A.*, **79**, 32095*g* (1973)].
3) W. Pfleiderer and H. Ferch, *Ann. Chem.*, **615**, 52 (1958).
4) After we completed the present work, R. Marumoto and Y. Furukawa reported the synthesis of this compound by another method: *Chem. Pharm. Bull.* (Tokyo), **25**, 2974 (1977).
5) F. Yoneda and M. Higuchi, *Bull. Chem. Soc. Japan*, **46**, 3849 (1973).
6) S. Nishigaki, K. Senga, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **19**, 1526 (1971).
7) Anthranils have been known to react with ammonium acetate under the conditions stated to give tricycloquinazolines: F. Yoneda and K. Mera, *Chem. Pharm. Bull.* (Tokyo), **21**, 1610 (1973).
8) W. Pfleiderer and G. Strauss, *Ann. Chem.*, **612**, 173 (1958).

the elimination of ammonia and formic acid.[9] Treatment of **2** with an excess of phosphorus pentasulfide in pyridine under reflux for 8 hr furnished 5,7-dimethyl-4-thioisoxazolo[3,4-*d*]-pyrimidine-4,6(5H,7H)-dione (**7**), instead of the expected isothiazolo[3,4-*d*]pyrimidine (**8**).[10] The structure of **7** was supported by the presence of a carbonyl absorption band at 1680 cm^{-1} in the infrared (IR) spectrum (Nujol) as well as by the previous findings that the initial thiation of 1,3-dimethyluracil fused heterocycles takes place at the position 4[11] (Chart 1).

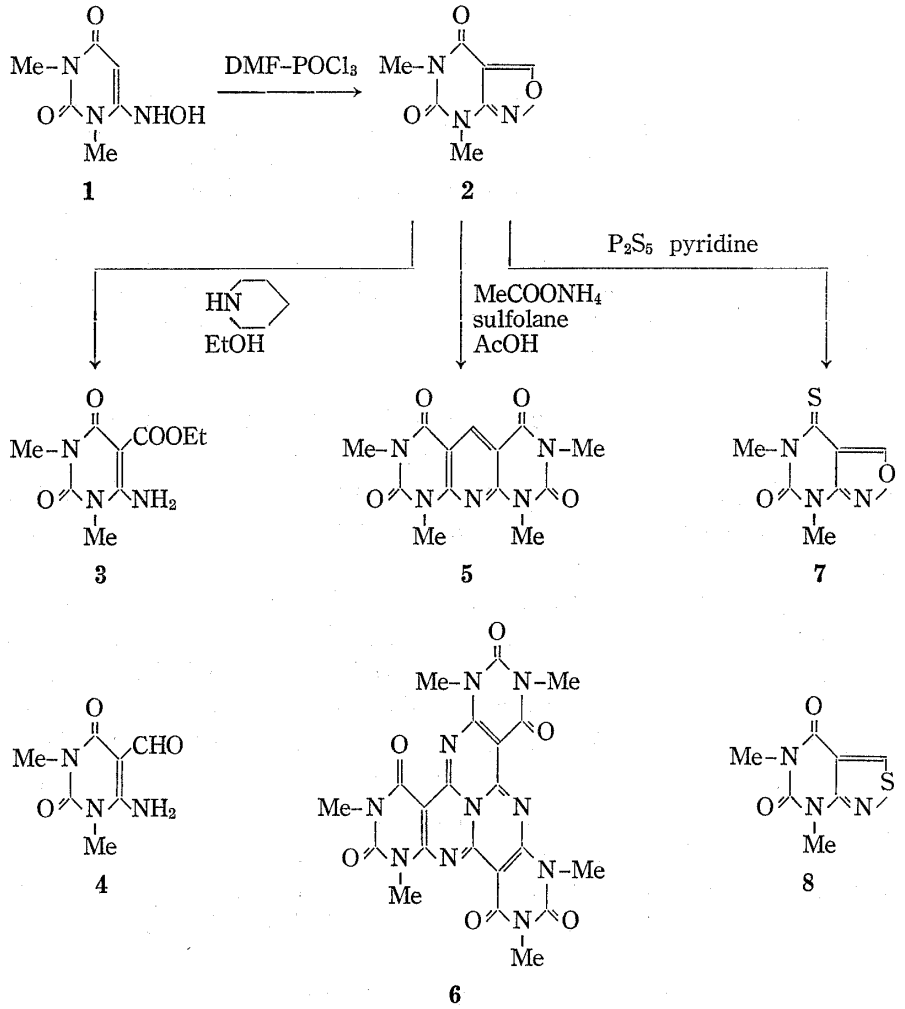


Chart 1

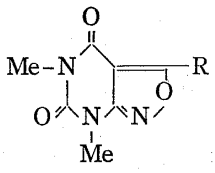
Refluxing of **1** with an excess of benzaldehyde in dimethylformamide for 2 hr provided 5,7-dimethyl-3-phenylisoxazolo[3,4-*d*]pyrimidine-4,6-(5H,7H)-dione (**10**)[4] in 34% yield. The NMR spectrum ($CDCl_3$) showed two singlets at δ 3.40 (N–Me) and 3.56 (N–Me), and a multiplet 7.46—7.73 (C^3–C_6H_5), while the mass spectrum revealed a parent ion at *m/e* 257. Analogously, the reaction of **1** with other arylaldehydes in dimethylformamide gave the corresponding 3-aryl-5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-diones (**11**—**17**) in 29—65% yields. As shown in the Table I, the yields of isoxazolo[3,4-*d*]pyrimidines were depending

9) In fact, the compound **5** can be obtained by refluxing of **4** with acetic acid; K. Senga and S. Nishigaki, unpublished result.

10) Anthranils have been reported to react with phosphorus pentasulfide to yield benzisothiazoles: O. Aki, Y. Nakagawa, and K. Shirakawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 2372 (1972).

11) For example: A. Kalmus and F. Bergmann, *J. Chem. Soc.*, **1960**, 3679; K.R.H. Wooldridge and R. Slack, *J. Chem. Soc.*, **1962**, 1863; F. Yoneda, Y. Sakuma, M. Ueno, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **21**, 926 (1973); K. Senga, M. Ichiba, and S. Nishigaki, *J. Org. Chem.*, **43**, 1677 (1978).

TABLE I. 5,7-Dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-diones



Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (Nujol) cm^{-1} (CO)	
2	H	171—172.5[a,c]	59	$C_7H_7N_3O_3$	46.41 (46.22	3.90 3.86	23.20 23.39)	1670	1720
10	C_6H_5	197—198[a,d]	34	$C_{13}H_{11}N_3O_3$	60.69 (60.50	4.31 4.30	16.34 16.47)	1665	1710
11	4-Br-C_6H_4	206—208[a]	47	$C_{13}H_{10}BrN_3O_3$	46.43 (46.24	2.99 2.94	12.51 12.56)	1670	1710
12	4-Cl-C_6H_4	191—192[a]	45	$C_{13}H_{10}ClN_3O_3$	53.52 (53.78	3.46 3.39	14.41 14.14)	1660	1710
13	4-NO_2-C_6H_4	>300[b]	65	$C_{13}H_{10}N_4O_5$	51.66 (51.93	3.34 3.47	18.54 18.50)	1655	1705
14	3,4-Cl_2-C_6H_3	275—276[b]	50	$C_{13}H_9Cl_2N_3O_3$	47.87 (47.78	2.79 2.81	12.89 12.66)	1655	1705
15	4-Me-C_6H_4	170—172[a]	29	$C_{14}N_{13}N_3O_3$	61.98 (62.09	4.83 4.66	15.49 15.75)	1660	1710
16	4-MeO-C_6H_4	183—184[a]	35	$C_{14}H_{13}N_3O_4$	58.53 (58.35	4.56 4.50	14.63 14.85)	1670	1715
17	3,4-$(MeO)_2$-C_6H_3	279—281[b]	38	$C_{15}H_{15}N_3O_5$	56.78 (56.54	4.77 4.62	13.24 13.40)	1653	1703

a) Recrystallized from EtOH.
b) Recrystallized from DMF.
c) Lit.[4] mp 170—171°.
d) Lit.[4] mp 195—196°.

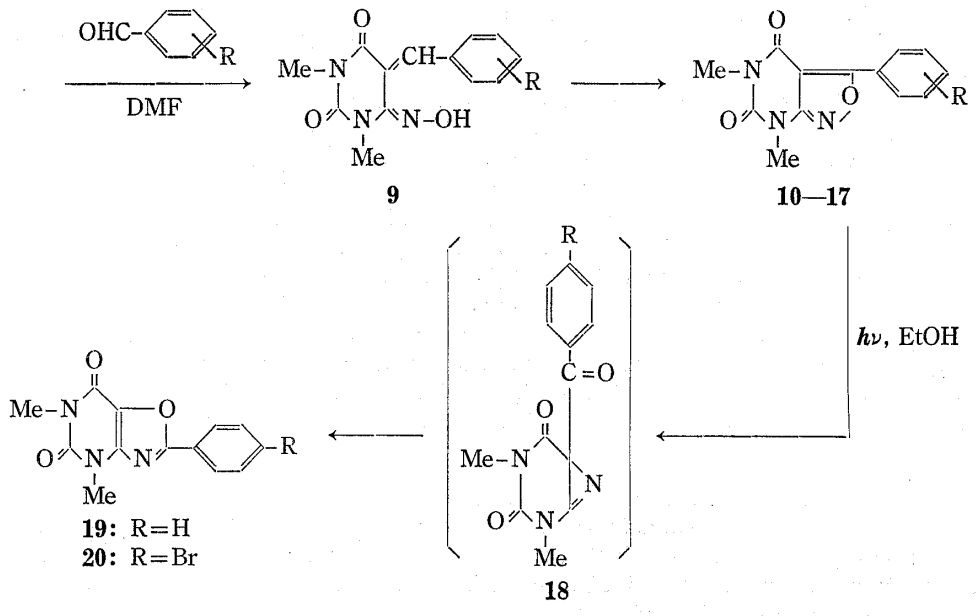


Chart 2

upon the nature of arylaldehyde employed. Thus, the arylaldehydes with an electron-withdrawing substituent gave better results than those with an electron-releasing substituent. This new isoxazolo[3,4-*d*]pyrimidines apparently involves the initial formation of a 5-benzylidene intermediate (**9**) and subsequent oxidative cyclization. The compounds **10**—**17** were stable against both acid and alkaline hydrolyses. For example, the treatment of **10** with 10% hydrochloric acid or ethanol containing piperidine under the conditions described in the case of **2** resulted in the quantitative recovery of the starting material in each case.

In connection with recent works in the photorearrangement of five-membered heterocycles,[12] we also investigated the photochemical behavior of the isoxazolo[3,4-*d*]pyrimidines. The photoirradiation of **10** in ethanol with a high pressure mercury lamp at 30° for 8 hr afforded 4,6-dimethyl-2-phenyloxazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (**19**) in 12% yield. The structure of **19** was ascertained by satisfactory elemental analysis and spectral data. In particular, the splitting of the phenyl protons into two multiplets by the ratio of 3: 2 in the NMR spectrum ($CDCl_3$) indicated that the phenyl group is attached to the α-position of the ring nitrogen. Likewise, the compound **11** was converted into the corresponding oxazolo-[4,5-*d*]pyrimidine (**20**) in a similar yield. This ring transformation can be best explained by assuming the initial formation of an aziridine intermediate (**18**) followed by recyclization as demonstrated previously in the photorearrangement of 3,5-diarylisoxazoles into 2,5-diaryloxazoles[12] (Chart 2).

Experimental[13]

5,7-Dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione (2) (Table I)——A mixture of 6-hydroxyamino-1,3-dimethyluracil (**1**)[3] (1.71 g, 0.01 mol) and the Vilsmeier reagent prepared from phosphorus oxychloride (3.06 g, 0.02 mol) and dry dimethylformamide (30 ml) was heated at 95° for 1 hr. The reaction mixture was evaporated *in vacuo* and the residue was suspended in H_2O (30 ml). The aqueous suspension was extracted with chloroform (3×50 ml) and the chloroform extracts were dried over sodium sulfate. Evaporation of chloroform and recrystallization of the residue gave pure **2** (0.97 g). MS *m/e*: 181 (M^+). NMR δ: 3.40 (s, 3H, N–Me), 3.54 (s, 3H, N–Me), 10.00 (s, 1H, C^3–H).

Ethyl 6-Amino-1,3-dimethyluracil-5-carboxylate (3)——A mixture of **2** (0.169 g, 0.0009 mol) and piperidine (3 drops) in ethanol (5 ml) was refluxed for 1 hr. The reaction mixture was evaporated *in vacuo* and the residue was covered with benzene. The insoluble crystals were filtered off and recrystallized from benzene to give pure **3** (0.155 g, 76%), mp 204—205°, identified with the authentic sample.[5]

1,3,7,9-Tetramethylpyrido[2,3-*d*, 6,5-*d'*]dipyrimidine-2,4,6,8-(1H, 3H, 7H, 9H)-tetrone (5)——A mixture of **2** (0.362 g, 0.002 mol) and ammonium acetate (0.308 g, 0.002 mol) in sulfolane (5 ml) containing AcOH (1 ml) was heated at 170° for 7 hr. The reaction mixture was diluted with H_2O (100 ml) and the precipitated crystals were filtered. Recrystallization from AcOH gave pure **5** (0.02 g, 7%), mp 320°, identified with the authentic sample.[6]

5,7-Dimethyl-4-thioisoxazolo[3,4-*d*]pyrimidine-4,6(5H, 7H)-dione (7)——A mixture of **2** (0.905 g, 0.005 mol) and phosphorus pentasulfide (3.33 g, 0.015 mol) in dry pyridine (10 ml) was refluxed for 8 hr. The reaction mixture was evaporated *in vacuo* and the residue was covered with boiling H_2O (50 ml). After cooling, the insoluble crystals were filtered off, washed well with hot H_2O and dried. Recrystallization from ethanol gave pure **7** (0.38 g, 39%), mp 164—165°. *Anal.* Calcd. for $C_7H_7N_3O_2S$: C, 42.61; H, 3.58; N, 21.32. Found: C, 42.70; H, 3.56; N, 21.54. MS *m/e*: 197 (M^+). IR cm^{-1}: 1680 (CO).

3-Aryl-5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5H, 7H)-diones (10—17) (Table I)——A mixture of **1** (0.0855 g, 0.0005 mol) and the appropriate arylaldehydes (0.001 mol) in dimethylformamide (3 ml) was refluxed for 2 hr. The reaction mixture was evaporated *in vacuo* and the residue was triturated with ethanol. The insoluble crystals were filtered off and recrystallized to provide the corresponding pure products **10**—**17**.

2-Aryl-4,6-dimethyloxazolo[4,5-*d*]pyrimidine-5,7(4H, 6H)-diones (19—20)——A suspension of the appropriate isoxazolo[3,4-*d*]pyrimidines (0.0005 mol) in ethanol (400 ml) was irradiated with a 100 W high

12) B. Singh and E.F. Ullman, *J. Am. Chem. Soc.*, **89**, 6911 (1967), and references cited therein.

13) Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Japan Spectroscopic Co., Ltd. spectrophotometer, Model IR-E from samples mulled in Nujol. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Mass spectra were performed on a JMS D100 EI spectrometer by a direct inlet system at 70 eV.

pressure mercury lamp surrounded by water-cooled Pyrex filter at 30° for 8—14 hr. The resulting solution was evaporated *in vacuo* and the residue was recrystallized from ethanol to give the corresponding pure products, respectively.

Compound **19**, mp 205—206° (0.016 g, 12%). *Anal.* Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.85; H, 4.32; N, 16.51. MS *m/e*: 257 (M^+). NMR δ: 3.45 (s, 3H, N–Me), 3.65 (s, 3H, N–Me), 7.40—7.67 (m, 3H, C^3–C_6H_5), 8.07—8.33 (s, 2H, C^3–C_6H_5). IR cm^{-1}: 1670, 1710 (CO).

Compound **20**, mp 214—216° (0.016 g, 10%). *Anal.* Calcd. for $C_{13}H_{10}BrN_3O_3$: C, 46.43; H, 2.99; N, 12.51. Found: C, 46.63; H, 3.03; N, 12.74. MS *m/e*: 335 (M^+). IR cm^{-1}: 1670, 1715 (CO).