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Pyrimidine Derivatives and Related Compounds. XL.¹⁾ Synthesis of 7-Substituted Pyrimido[5,4-*d*]pyrimidines

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5-Amino-1,3-dimethyl-6-(substituted amino)methyluracils (**3a—d**) prepared by the reduction of 1,3-dimethyl-5-nitro-6-(substituted amino)methyluracils (**2a—d**) were treated with triethyl orthoformate to give the corresponding 7-substituted pyrimido[5,4-*d*]pyrimidines (**7a—d**) in good yields. Treatment of **3a** with dimethylformamide dimethyl acetal afforded a 5-dimethylaminomethylenamino intermediate (**6**), which cyclized to **7a** on heating in toluene.

Keywords—pyrimido[5,4-*d*]pyrimidine; cyclization with triethyl orthoformate; reduction of nitro group; NMR; dimethylformamide dimethyl acetal

In the preceding papers,²⁻⁴⁾ we reported the convenient synthesis of 2-substituted pyrazolo[4,3-*d*]pyrimidine 1-oxides²⁾ and their ring transformation into 6-substituted pyrimido[5,4-*d*]pyrimidines.³⁾ Our interest in the possible physiological activity of pyrimido[5,4-*d*]pyrimidines as deaza and aza analogs of pteridine, led us to investigate a convenient method for the synthesis of such a heterocyclic system. To date, although many pyrimido[5,4-*d*]pyrimidine derivatives have been prepared⁵⁾ in connection with studies of the coronary vasodilative activity of dipyridamole,⁶⁾ the principal synthetic method is only condensation of 5-amino-4-carboxypyrimidines with C-N (or N-C-N) fragment reagents.⁷⁾ In this paper we wish to report a new and facile synthesis of 7-substituted pyrimido[5,4-*d*]pyrimidines using readily available 6-bromomethyl-1,3-dimethyl-5-nitrouracil (**1**)⁸⁾ as a starting material.

1,3-Dimethyl-5-nitro-6-(substituted amino)methyluracils (**2a—d**) were prepared by the reaction of **1** with primary amines.^{2,4)} Conversion of the nitro group of **2** into an amino group was investigated by dithionite and catalytic reductions. Thus, treatment of **2a** with sodium dithionite in 50% ethanol at 80°C afforded two products; one was the expected 5-amino derivative (**3a**) and the other was 4,6-dimethyl-2-phenyl-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*, 6*H*)-dione (**4**). The structure of **4** was confirmed by direct comparison with a sample prepared by catalytic reduction of the corresponding N-oxide (**5**).

The reaction mechanism for the formation of **4** presumably involves cyclization of **2a** and subsequent reduction of **5**, as reported previously.²⁾ Similar reduction of **2c** gave only the 5-aminouracil (**3c**) in 44% yield. On the other hand, catalytic reduction of **2a—d** at room temperature and atmospheric pressure over palladium on charcoal gave the corresponding 5-aminouracils (**3a—d**) in much better yields (see Table I).

One-carbon (C₁) reagents, such as triethyl orthoformate and N,N-dimethylformamide dimethyl acetal (DMFDMA) are extensively employed for the synthesis of fused heterocycles.⁹⁾ We examined the cyclization of **3** using such C₁ reagents. Thus, when compound **3a** and DMFDMA were heated at reflux temperature for 5 minutes, a condensation product, 5-dimethylaminomethylenamino derivative (**6**) was formed in 73% yield. Further heating of **6** in DMFDMA resulted in its recovery unchanged, but in toluene afforded the expected pyrimido[5,4-*d*]pyrimidine (**7a**) in 89% yield. On the other hand, refluxing of **3a** and triethyl orthoformate directly caused ring closure without isolation of an intermediate (**8**) to give **7a** in 84% yield. Similar treatment of **3b—d** with triethyl orthoformate gave the corresponding pyrimido[5,4-*d*]pyrimidines (**7b—d**) in high yields (Table II). The structures of **7a—d** were

established by their spectral data (Table III).

Experimental

Melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^1H -Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi Perkin-Elmer R-20B 60 MHz spectrometer with tetramethylsilane as an internal standard. Infrared (IR) spectra were obtained from KBr pellets with a Hitachi 215 instrument. Ultraviolet (UV) spectra were measured on a Hitachi 323 spectrophotometer.

5-Amino-1,3-dimethyl-6-(substituted amino)methyluracils (3a—d) (Table I)—General Procedure: To a suspension of 2a—d (1.0 g) in methanol (150 ml) was added 0.2 g of palladium on charcoal, and the mixture was shaken under an H_2 stream (1 atm) at room temperature. After H_2 absorption had ceased, the reaction mixture was heated and the hot solution was filtered to remove the catalyst. The filtrate was evaporated to dryness *in vacuo*, and ethanol and ether were added to the residue. The resulting precipitate was collected by filtration to give 3a—d.

TABLE I. 5-Amino-1,3-dimethyl-6-(substituted amino)methyluracils (3a—d)

Compd.	R	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%)		
						Calcd		Found
						C	H	N
3a	C ₆ H ₅	61	189—191	EtOH	C ₁₃ H ₁₆ N ₄ O ₂	59.89 (60.00)	6.20 6.04	21.53 21.43
3b	C ₆ H ₄ OCH ₃ (<i>p</i>)	51	187—189 (dec.)	MeOH	C ₁₄ H ₁₈ N ₄ O ₃	57.92 (58.10)	6.25 6.17	19.30 19.40
3c	C ₆ H ₄ CH ₃ (<i>p</i>)	58(44) ^{a)}	195—197	MeOH	C ₁₄ H ₁₈ N ₄ O ₂	61.29 (61.36)	6.61 6.53	20.43 20.27
3d	CH ₂ C ₆ H ₅	31	89— 90	Ether	C ₁₄ H ₁₈ N ₄ O ₂	61.29 (61.37)	6.61 6.66	20.43 20.55

a) Reduced with sodium dithionite.

Reduction of 2a with Sodium Dithionite—Sodium dithionite (1.8 g, 0.01 mol) was gradually added to a suspension of **2a** (1.0 g, 0.0034 mol) in water (10 ml) at 90°C with stirring. The mixture was cooled, and the resulting precipitate was collected by filtration and recrystallized fractionally from ethanol to give 0.2 g (23%) of **3a** (which was identical with the sample prepared above) and 0.06 g (7%) of **4**. Compound **4**: mp 248–249°C (from ethanol). *Anal.* Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 61.08; H, 4.68; N, 22.00. IR $\nu_{\max}$ cm^{-1} : 1710, 1660 (C=O). NMR (DMSO- d_6) δ : 3.28 (3H, s, NCH₃), 3.39 (3H, s, NCH₃), 7.40–8.07 (5H, m, C₆H₅), 8.76 (1H, s, CH=).

Reduction of 2c with Sodium Dithionite—Sodium dithionite (1.8 g, 0.01 mol) was gradually added to a suspension of **2c** (1.0 g, 0.003 mol) in 50% ethanol (50 ml) at 80°C with stirring. Heating was continued for a further 10 min, and the resulting precipitate was collected by filtration to give 400 mg (44%) of **3c**, which was identical with the sample prepared above.

4,6-Dimethyl-2-phenyl-2H-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (4)—A suspension of **5^a** (450 mg) and palladium on charcoal (200 mg) in methanol (200 ml) was shaken under an H₂ stream (1 atm) at room temperature. After H₂ absorption had ceased, the catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. Methanol and ether were added to the residue. The resulting precipitate was collected by filtration to give 245 mg (58%) of **4**, which was identical with the sample obtained above.

6-Anilinomethyl-5-dimethylaminomethylenamino-1,3-dimethyluracil (6)—A mixture of **3a** (260 mg, 1 mmol) and dimethylformamide dimethyl acetal (1 ml) in dimethylformamide (DMF) (1 ml) was refluxed for 5 min. Ether (30 ml) was added to the reaction mixture and the resulting precipitate was filtered off. Recrystallization from ethanol gave 230 mg (73%) of **6**, mp 125°C. *Anal.* Calcd for $C_{16}H_{21}N_5O_2$: C, 60.93; H, 6.71; N, 22.21. Found: C, 61.01; H, 6.64; N, 21.99. IR $\nu_{\max}$ cm^{-1} : 3350 (NH), 1695, 1660 (C=O). NMR (CDCl₃) δ : 2.94 (6H, s, N(CH₃)₂), 3.48 (3H, s, NCH₃), 3.53 (3H, s, NCH₃), 4.46 (2H, s, CH₂), 6.60–7.45 (5H, m, C₆H₅), 8.37 (1H, s, N=CH).

7-Substituted 7,8-Dihydro-1,3-dimethylpyrimido[5,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (7a–d) (Table II and III)—A mixture of **3a–d** (0.001 mol) and triethyl orthoformate (5 ml) was refluxed for 3 h. Ether was added to the reaction solution and the resulting precipitate was separated by filtration. The product was recrystallized from an appropriate solvent as given in Table II.

TABLE II. 7-Substituted 7,8-Dihydro-1,3-dimethylpyrimido[5,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (7a–d)

Compd.	R	Yield (%)	mp (dec., °C)	Recryst. solvent	Formula	Analysis (%)		
						Calcd	Found	
						C	H	N
7a	C ₆ H ₅	84	208–210	MeOH	C ₁₄ H ₁₄ N ₄ O ₂	62.21 (61.99)	5.22 5.12	20.71 20.61
7b	C ₆ H ₄ OCH ₃ (<i>p</i>)	89	177–179	MeOH	C ₁₅ H ₁₆ N ₄ O ₃	59.99 (59.88)	5.37 5.26	18.66 18.63
7c	C ₆ H ₄ CH ₃ (<i>p</i>)	96	187–189	MeOH	C ₁₅ H ₁₆ N ₄ O ₂	63.36 (63.65)	5.67 5.63	19.71 19.66
7d	CH ₂ C ₆ H ₅	91	198	EtOH	C ₁₅ H ₁₆ N ₄ O ₂	63.36 (63.46)	5.67 5.69	19.71 19.69

TABLE III. Spectroscopic Properties of Pyrimido[5,4-*d*]pyrimidines (7a–d)

Compd.	IR $\nu_{\max}$ C=O	UV $\lambda_{\max}$ (ε)	NMR δ (ppm)			
			C ₆ -H	CH ₂ N	NCH ₃	Others
7a	1700 1660	267(19300), 345 sh(7700), 356(8100)	8.17 ^{a)}	5.33	3.55	7.50 (5H, m, aromatic)
7b	1700 1660	272(20900), 356(8000)	8.14 ^{a)}	5.31	3.53	3.94 (3H, s, OCH ₃), 7.28 (4H, m, aromatic)
7c	1700 1650	269(20700), 348 sh(7800), 358(8200)		4.80 ^{b)}	3.36 3.40	2.36 (3H, s, CH ₃), 7.05 (5H, m, C ₆ -H and aromatic)
7d	1700 1650	239 sh(7800), 265(11000), 337 sh(4100), 348(4400)	7.09 ^{b)}	4.33	3.23 3.35	4.29 (2H, s, CH ₂), 7.34 (5H, s, aromatic)

a) CF₃COOD solutions, b) CDCl₃ solutions.

7,8-Dihydro-1,3-dimethyl-7-phenylpyrimido[5,4-*d*]pyrimidine-2,4 (1*H*,3*H*)-dione (7a)—A suspension of **6** (100 mg) in toluene (20 ml) was refluxed for 3 h. The solution was allowed to stand at room temperature, then the precipitate was filtered off and dried to give 76 mg (89%) of **7a**, which was identical with the sample prepared above.

References and Notes

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Shape-transforming Action of Myrmicacin (3-Hydroxydecanoic Acid) and Some Related Compounds on the Membrane of Intact Human Erythrocytes

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The effects of the following compounds (most of which had been proved to inhibit mitotic progression of pollens) on the shape of the membrane of human erythrocytes were tested: myrmicacin (3-hydroxydecanoic acid) and its derivatives, even-numbered C₄₋₁₀ fatty acids, and some C₁₀ diols. They all induced a shape change of the membrane-exvagination (crenation) type at pH 7.4 to different extents, depending on their structures, but not at pH 6.0. The shape change induced was reversible. The structure-activity relationship and the mode of action were compared with those for the action of these compounds on pollen growth.

Keywords—membrane shape change; human erythrocytes; myrmicacin; fatty acids; transforming activity; crenation; mitotic progression

Introduction

One of the authors (Iwanami) found that 3-hydroxydecanoic acid (myrmicacin), present in secretions of a leaf-cutting ant, reversibly inhibits the mitotic progression of *Ornithogalum virens* pollens at any stage.¹⁾ Further studies revealed that certain carboxylic acids structurally related to myrmicacin also have a similar effect on pollens from various plant species,²⁻⁴⁾