Chem. Pharm. Bull. 29(10)3060—3063(1981)

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

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(Received April 20, 1981)

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-oxides[2] 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 prepared[5] 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 (C_1) 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 C_1 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

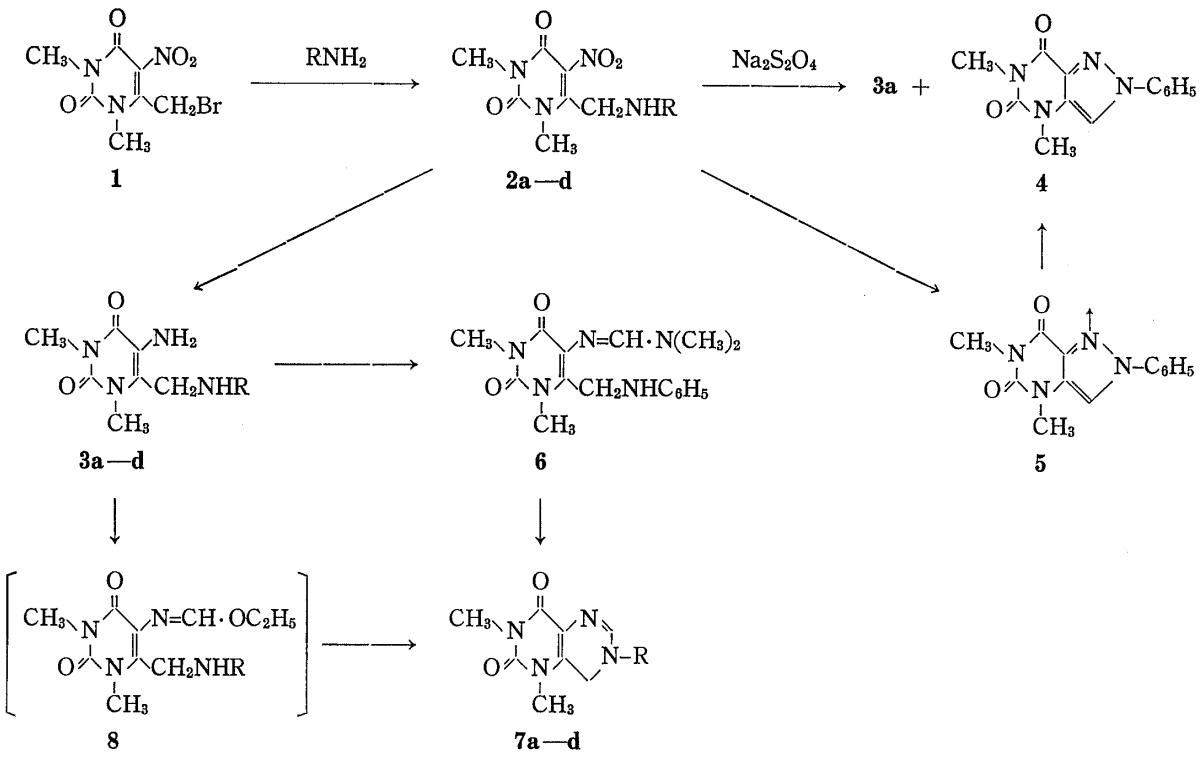

Chart 1

established by their spectral data (Table III).

Experimental

Melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^{1}H-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 solutipn 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_6H_5	61	189—191	EtOH	$C_{13}H_{16}N_4O_2$	59.89 (60.00	6.20 6.04	21.53 21.43)
3b	$C_6H_4OCH_3(p)$	51	187—189 (dec.)	MeOH	$C_{14}H_{18}N_4O_3$	57.92 (58.10	6.25 6.17	19.30 19.40)
3c	$C_6H_4CH_3(p)$	58(44)[a]	195—197	MeOH	$C_{14}H_{18}N_4O_2$	61.29 (61.36	6.61 6.53	20.43 20.27)
3d	$CH_2C_6H_5$	31	89— 90	Ether	$C_{14}H_{18}N_4O_2$	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 ν_{max} cm^{-1}: 1710, 1660 (C=O). NMR (DMSO-d_6) δ: 3.28 (3H, s, NCH_3), 3.39 (3H, s, NCH_3), 7.40—8.07 (5H, m, C_6H_5), 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-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (4)——A suspension of **5**[4] (450 mg) and palladium on charcoal (200 mg) in methanol (200 ml) was shaken under an H_2 stream (1 atm) at room temperature. After H_2 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 ν_{max} cm^{-1}: 3350 (NH), 1695, 1660 (C=O). NMR ($CDCl_3$) δ: 2.94 (6H, s, $N(CH_3)_2$), 3.48 (3H, s, NCH_3), 3.53 (3H, s, NCH_3), 4.46 (2H, s, CH_2), 6.60—7.45 (5H, m, C_6H_5), 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_6H_5	84	208—210	MeOH	$C_{14}H_{14}N_4O_2$	62.21 (61.99	5.22 5.12	20.71 20.61)
7b	$C_6H_4OCH_3(p)$	89	177—179	MeOH	$C_{15}H_{16}N_4O_3$	59.99 (59.88	5.37 5.26	18.66 18.63)
7c	$C_6H_4CH_3(p)$	96	187—189	MeOH	$C_{15}H_{16}N_4O_2$	63.36 (63.65	5.67 5.63	19.71 19.66)
7d	$CH_2C_6H_5$	91	198	EtOH	$C_{15}H_{16}N_4O_2$	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 ν_{max} C=O	UV λ_{max} (ε)	NMR δ(ppm) C_6–H	CH_2N	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) CF_3COOD solutions, *b*) $CDCl_3$ 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

1) For part XXXIX: see K. Hirota, Y. Kitade, and S. Senda, *J. Org. Chem.*, in press.
2) S. Senda, K. Hirota, T. Asao, and Y. Yamada, *Chem. Commun.*, **1977**, 556.
3) S. Senda, K. Hirota, T. Asao, and Y. Yamada, *Tetrahedron Lett.*, **1978**, 2295.
4) K. Hirota, Y. Yamada, T. Asao, and S. Senda, *J. Chem. Soc. Perkin I*, in press.
5) For example, see F.G. Fischer, W.P. Neumann, and J. Roch, *Ann.*, **633**, 158 (1960); K. Thomae, Brit. Patent 807829 (1959) [*C.A.*, **53**, 12317 (1959)].
6) M. Windholz (ed.), "The Merck Index," 9th ed., Merck and Co., Inc., Rahway, N.J., 1976, p. 448; V.R. Kadatz, *Arzneimittel-Forsch.*, **9**, 39 (1959).
7) F.G. Fischer and J. Roch, *Ann.*, **572**, 217 (1951).
8) K. Hirota, Y. Yamada, T. Asao, and S. Senda, *J. Chem. Soc., Perkin I*, **1981**, 1896.
9) For example, see S. Nishigaki, M. Ichiba, J. Sato, K. Senga, M. Noguchi, and F. Yoneda, *Heterocycles*, **9**, 11 (1978); S. Nishigaki, J. Sato, K. Shimizu, K. Furukawa, K. Senga, and F. Yoneda, *Chem. Pharm. Bull.*, **28**, 142 (1980).

[Chem. Pharm. Bull. 29(10)3063—3066(1981)]

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

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(Received December 22, 1980)

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 C_{4-10} fatty acids, and some C_{10} 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]