Notes

[Chem. Pharm. Bull. 26(10)3208—3211(1978)]

UDC 547.854.4.04 : 546.268.1.04

Pyrimidine Derivatives and Related Compounds. XXX.[1] Synthesis and Some Reactions of 5,6-Dicyano-1,3-dimethyluracil[2]

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(Received March 20, 1978)

5,6-Dicyano-1,3-dimethyluracil (**1**) was synthesized stepwise from 6-chloro-5-formyl-1,3-dimethyluracil (**2**). Treatment of **1** with butylamine or aniline afforded 6-butylamino- (**5**) or 6-anilino-5-cyano-1,3-dimethyluracil (**6**), respectively. 3-Amino-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5H, 7H)-dione (**7**) was obtained by the reaction of **1** with hydrazine hydrate. When **1** was refluxed in methanol in the presence of a catalytic amount of sodium methoxide, 5-cyano-6-methoxy-1,3-dimethyluracil (**9**) was obtained. Acid hydrolysis of **1** afforded 6-carbamoyl-1,3-dimethylorotic acid (**10**).

Keywords——nucleophilic substitution; acid hydrolysis; reaction of cyano group; 5,6-dicyanouracils; pyrazolo[3,4-*d*]pyrimidine synthesis

In the previous papers,[4–9] we reported the syntheses and reactions of cyanouracils, in which 6-cyanouracils show interesting behaviors towards nucleophiles compared with 5-cyanouracils. The 6-cyanouracils undergo rearrangement to the 5-position, substitution at the 6-position, or addition to the C≡N bond, depending on a property of the nucleophiles employed and the reaction conditions applied.[6,7] In order to clarify the difference of the reactivities toward nucleophiles between the 5- and the 6-cyano group in the same molecule, we have synthesized 5,6-dicyano-1,3-dimethyluracil (**1**) and studied its reactions it with some nucleophiles.

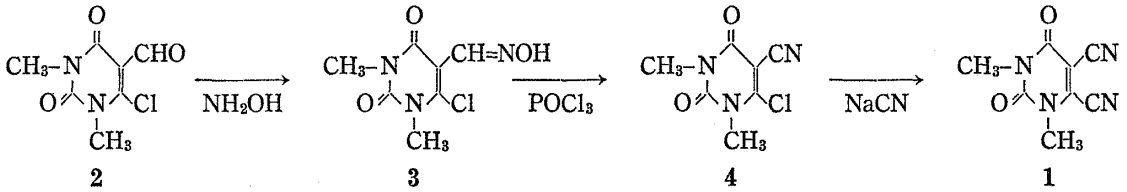

Chart 1

5,6-Dicyano-1,3-dimethyluracil (**1**) was synthesized stepwise from 6-chloro-5-formyl-1,3-dimethyluracil (**2**).[10] Treatment of **2** with hydroxylamine in methanol afforded 6-chloro-1,3-dimethyluracil-5-carbaldehyde oxime (**3**), followed by dehydration of **3** with phosphorous

1) Part XXIX: S. Senda, K. Hirota, M. Suzuki, and M. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **25**, 563 (1977).
2) A part of this work was presented at the 7th Congress of Heterocyclic Chemistry, Chiba, 1974 (Abstracts of Papers, p. 140).
3) Location: *Mitahora-Higashi, Gifu 502, Japan.*
4) S. Senda, K. Hirota, and J. Notani, *Chem. Pharm. Bull.* (Tokyo), **20**, 1380 (1972).
5) S. Senda, K. Hirota, and J. Notani, *Chem. Pharm. Bull.* (Tokyo), **20**, 1389 (1972).
6) S. Senda, K. Hirota, and T. Asao, *J. Org. Chem.*, **40**, 353 (1975).
7) S. Senda, K. Hirota, and T. Asao, *Chem. Pharm. Bull.* (Tokyo), **23**, 1708 (1975).
8) S. Senda, K. Hirota, and T. Asao, *Yakugaku Zasshi*, **95**, 1250 (1975).
9) S. Senda, K. Hirota, and T. Asao, *Heterocycles*, **3**, 213 (1975).
10) S. Senda, K. Hirota, G.-N. Yang, and M. Shirahashi, *Yakugaku Zasshi*, **91**, 1372 (1971).

oxychloride to give 6-chloro-5-cyano-1,3-dimethyluracil (**4**). Reaction of **4** with sodium cyanide was carried out in dry dimethylsulfoxide (DMSO) to yield the dinitrile (**1**).

When **1** was refluxed in neat butylamine for 1 hr, 6-butylamino-5-cyano-1,3-dimethyluracil (**5**) was obtained in quantitative yield. Refluxing of **1** with aniline in methanol led to a similar substitution giving 6-anilino-5-cyano-1,3-dimethyluracil (**6**) in 88% yield. Treatment of **1** with hydrazine hydrate afforded 3-amino-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6-(5H,7H)-dione (**7**) in quantitative yield. This conversion would also involve a nucleophilic substitution of the 6-cyano group with hydrazine hydrate resulting 5-cyano-6-hydrazino-1,3-dimethyluracil (**8**) as an intermediate, followed by cyclization to **7**.

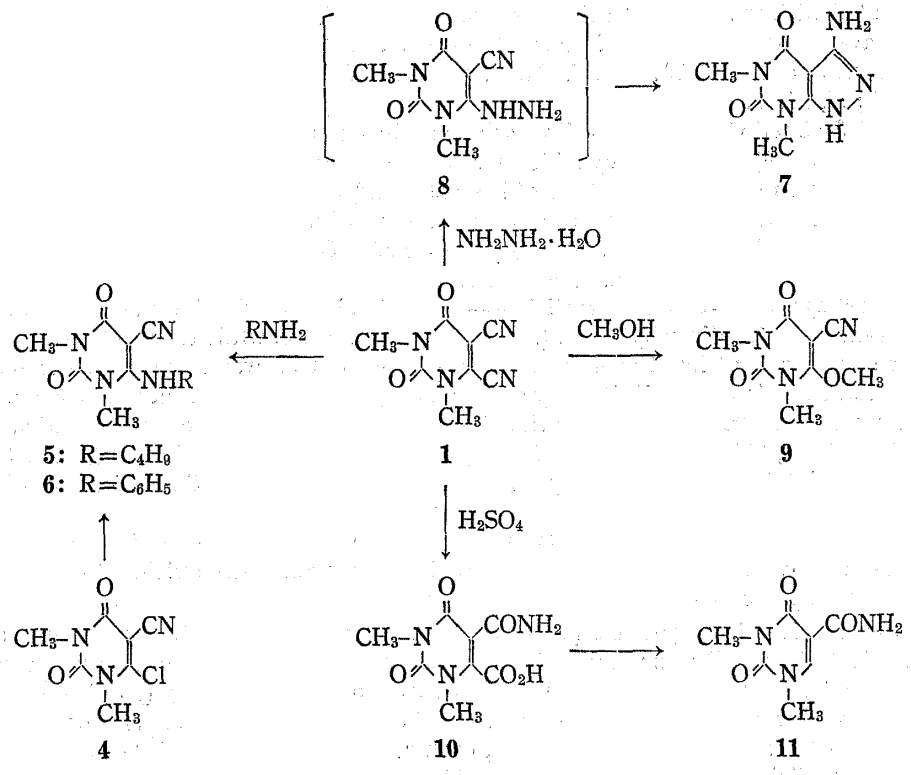

Chart 2

It is not abnormal that the 6-cyano group of the dinitrile (**1**) undergo the nucleophilic substitution in the presence of strong nucleophiles such as amines and hydrazine hydrate, because we have found[7] that reaction of 6-cyano-1,3-dimethyluracil with butylamine or hydrazine hydrate gives 6-butylamino- or 6-hydrazino-1,3-dimethyluracil, respectively. Furthermore, the facility of the nucleophilic substitution at the 6-cyano group was observed even in the absence of strong nucleophiles. Thus, on refluxing of **1** in methanol in the presence of a catalytic amount of sodium methoxide, replacement of the 6-cyano group with methanol occurred to give 5-cyano-6-methoxy-1,3-dimethyluracil (**9**) in 42% yield. Addition of methanol to the C≡N bond did not take place and such an adduct as the imidate obtained from 6-cyano-1,3-dimethyluracil[7] under the same conditions was not detected. All the 6-substituted products described here were independently prepared from 6-chloro-5-cyano-1,3-dimethyluracil (**4**) and the corresponding nucleophiles, and their structures were fully confirmed.

Acid hydrolysis of the 5,6-dicyanouracil (**1**) using conc. sulfuric acid let to the formation of 5-carbamoyl-1,3-dimethylorotic acid (**10**). The structure of **10** was confirmed by its decarboxylation to the known[11] 1,3-dimethyluracil-5-carboxamide (**11**).

11) W. Liebenow and H. Liedtke, *Chem. Ber.*, **105**, 2095 (1972).

Experimental[12]

6-Chloro-1,3-dimethyluracil-5-carbaldehyde Oxime (3)——To a stirring suspension of 7.0 g (0.1 mol) of hydroxylamine hydrochloride and 16.2 g (0.08 mol) of 6-chloro-5-formyl-1,3-dimethyluracil (2)[10] in methanol (150 ml) was added dropwise over a period of 1 hr a solution of 5.6 g (0.1 mol) of potassium hydroxide in 10 ml of water, while the reaction mixture was maintained below 10°. The mixture was stirred at room temperature for 1 hr, and the resulting precipitate was collected by filtration and washed with water to give 24.8 g (98%) of 3, mp 134—135°. The analytical sample, recrystallized from methanol, melted at 139—140°. *Anal.* Calcd. for $C_7H_8ClN_3O_3$: C, 38.74; H, 3.72; N, 19.37. Found: C, 38.89; H, 3.97; N, 19.21.

6-Chloro-5-cyano-1,3-dimethyluracil (4)——To 200 ml of phosphorous oxychloride was gradually added 22 g (0.1 mol) of 3 at room temperature with stirring. After stirring for 2 hr at room temperature, the solution was evaporated to dryness under reduced pressure. The residue was washed with ether several times and triturated with water. Filtration then gave 14 g (70%) of the crude product. Recrystallization from methanol gave colorless needles of 4, mp 171—172°. IR ν_{max} cm^{-1}: 2240 (CN). NMR ($CDCl_3$) δ: 3.37 and 3.68 (each s, each NCH_3). *Anal.* Calcd. for $C_7H_6ClN_3O_2$: C, 42.13; H, 3.03; N, 21.06. Found: C, 42.34; H, 3.07; N, 21.19.

5,6-Dicyano-1,3-dimethyluracil (1)——To a stirring solution of 5 g (0.025 mol) of 4 in dry DMSO (20 ml) was added 1.5 g (0.03 mol) of sodium cyanide at room temperature. After stirring at room temperature for 3 hr, the mixture was poured into 100 ml of ice-water and the precipitate was collected by filtration to give 2.5 g (43%) of 1. Recrystallization from ethanol gave colorless leaflets of 1, mp 182—185°. IR ν_{max} cm^{-1}: 2240 (CN). NMR ($CDCl_3$) δ: 3.32 and 3.65 (each s, each NCH_3). *Anal.* Calcd. for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.47. Found: C, 50.77; H, 3.29; N, 29.31.

6-Butylamino-5-cyano-1,3-dimethyluracil (5)——a) To 5 ml of butylamine was added dropwise 500 mg (2.6 mmol) of 5,6-dicyano-1,3-dimethyluracil (1) at room temperature, while the reaction proceeded exothermically. After standing for 1 hr at room temperature, the solution was removed under reduced pressure to give the oily residue which was solidified by addition of ether. Filtration then gave 610 mg (99%) of the crude product, mp 185—200°. Recrystallization from methanol gave colorless needles of 5, mp 199—201°. IR ν_{max} cm^{-1}: 2200 (CN), 3350 (NH). NMR ($CDCl_3$) δ: 0.73—1.40 (7H, m, $NCH_2\underline{C_3H_7}$), 3.15 and 3.40 (each 3H, each s, each $N\underline{CH_3}$), 3.72 (2H, m, $N\underline{CH_2}C_3H_7$), 7.06 (1H, bs, NH). *Anal.* Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.91; H, 6.83; N, 23.72. Found: C, 55.98; H, 6.86; N, 23.81.

b) 6-Chloro-5-cyano-1,3-dimethyluracil (4) (500 mg, 2.5 mmol) was treated in 5 ml of butylamine according to the same procedure as described above to give 5 in quantitative yield which was identical with the product prepared by the procedure (a).

6-Anilino-5-cyano-1,3-dimethyluracil (6)——a) A mixture of 480 mg (2.5 mmol) of 1 and 470 mg (5 mmol) of aniline in DMF (5 ml) was refluxed for 15 min. After cooling, the mixture was poured into 50 ml of ether and the resulting precipitate was collected by filtration to give 560 mg (88%) of the crude product. Recrystallization from ethanol gave colorless needles of 6, mp 280—281°. IR ν_{max} cm^{-1}: 2220 (CN), 3250 (NH). NMR (DMSO-d_6) δ: 3.15 and 3.40 (each 3H, each s, each NCH_3), 7.23—7.42 (5H, m, aromatic), 9.43 (1H, bs, NH). *Anal.* Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 61.90; H, 4.69; N, 21.89.

b) A mixture of 500 mg (2.5 mmol) of 4 and 460 mg of aniline in methanol (20 ml) was refluxed for 1 hr. The solvent was evaporated *in vacuo* and the residue was treated with water. The resulting precipitate was collected by filtration to give the crude product of 6 (90% yield) which was identical with the product prepared by the procedure (a).

3-Amino-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione (7)——a) To a solution of 480 mg (2.5 mmol) of 1 in methanol (10 ml) was added 10 ml of methanolic solution containing 250 mg (5 mmol) of hydrazine hydrate at room temperature, while the reaction proceeded exothermically. After standing for 2 hr, the resulting precipitate was collected by filtration to give 460 mg (94%) of the crude product. Recrystallization from methanol gave colorless needles of 7, mp>300°, NMR (DMSO-d_6) δ: 3.13 and 3.25 (each 3H, each s, each NCH_3), 6.22 (2H, bs, NH_2), 11.53 (1H, bs, NH). *Anal.* Calcd. for $C_7H_9N_5O_2$: C, 43.07; H, 4.65; N, 35.89. Found: C, 42.81; H, 4.64; N, 35.67.

b) A mixture of 500 mg (2.5 mmol) of 4 and 250 mg of hydrazine hydrate was treated according to the procedure as described above to give 430 mg (88%) of 7, which was identical with the product prepared by the procedure (a).

5-Cyano-6-methoxy-1,3-dimethyluracil (9)——a) To a solution of 480 mg (2.5 mmol) of 1 in 10 ml of methanol was added sodium methoxide, prepared from 6 mg (0.2 mmol) of sodium in 1 ml of absolute methanol. The mixture was refluxed for 30 min and allowed to stand for overnight. The resulting precipitate

12) Melting points were taken on a Yanagimoto Micro Melting Point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrophotometer as KBr pellets. Nuclear magnetic resonance (NMR) spectra were measured on a Hitachi Perkin-Elmer R-20B spectrometer using tetramethylsilane as internal standard.

was collected by filtration to give 200 mg (41%) of the crude product. Recrystallization from methanol gave colorless needles of **9**, mp 165—167°. IR ν_{max} cm^{-1}: 2220 (CN). NMR ($CDCl_3$) δ: 3.34 and 3.42 (each 3H, each s, each NCH_3), 4.53 (3H, s, OCH_3). *Anal.* Calcd. for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.32; H, 4.65; N, 21.55.

b) A mixture of 500 mg (2.5 mmol) of **4** and 140 mg (2.6 mmol) of sodium methoxide in 10 ml of methanol was refluxed for 30 min. After cooling, the resulting precipitate was collected by filtration to give the crude product of **9** (86% yield) which was identical with the product prepared by the procedure (a).

5-Carbamoyl-1,3-dimethylorotic Acid (10)——A suspension of 480 mg (2.5 mmol) of **1** in 4 ml of conc. sulfuric acid was heated at 60—70° for 1 hr. After cooling, the mixture was poured into 50 ml of water and allowed to stand for a week. The resulting precipitate was collected by filtration to give 330 mg (58%) of the crude product. Recrystallization from methanol to give colorless prisms of **10**, mp 164—166°. NMR (DMSO-d_6) δ: 3.20 and 3.43 (each 3H, each s, each NCH_3), 7.49 and 8.18 (each 1H, each bs, $CONH_2$), 8.50 (1H, s, OH). *Anal.* Calcd. for $C_8H_9N_3O_5$: C, 42.29; H, 3.99; N, 18.50. Found: C, 42.00; H, 4.05; N. 18.23.

1,3-Dimethyluracil-5-carboxamide (11)——A suspension of 200 mg (0.9 mmol) of **10** in diphenyl ether (2 ml) was refluxed for 10 min. After cooling, the mixture was diluted with ether and the resulting precipitate was collected by filtration to give 100 mg (61%) of the crude product. Recrystallization from water gave colorless needles of **11**, mp 219—220° (lit.[11] mp 216—218°), which was identical with an authentic sample.[11]

[Chem. Pharm. Bull. 26(10)3211—3214(1978)]

UDC 547.818.1.04 : 547.582.04

The Roles of Hetero Atoms in Solvolytic Reactions V[1] Transannular β-S-Participation in Solvolysis of S-Containing Heterocycles

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(Received March 28, 1978)

The *p*-nitrobenzoates of 2-methyltetrahydro-2-thiophenemethanol and 3-methyltetrahydro-3-thiopyranol have been synthesized. The rates of solvolysis of the esters in 80% aqueous acetone have been determined titrimetrically. The β-methyl substitution of the primary ester has caused the rate to increase by a factor of 28 and its rate is 3.9 times faster than that of the tertiary ester. Both esters yield the corresponding alcohols in similar ratio, so that it is concluded to intervene the same intermediary episulfonium ion.

Keywords——S-containing 5- and 6-membered heterocycles; solvolysis; neighboring group participation by divalent sulfur; rate enhancement; episulfonium ion

Neighboring group participation of the sulfur atom in solvolytic reactions, which is usually observed as unexpectedly large effect,[3] provides valuable information to mechanistic studies.[1,4] An episulfonium ion intervening in the chemical conversion of penam to cephem[5] gives us much interests in the direction of its ring-opening. In connection with this skeletal

1) Part IV in this series: J. Ohishi, K. Tsuneoka, S. Ikegami, and S. Akaboshi, *J. Org. Chem.*, in press.
2) Location: *9-1, Anagawa-4-chome, Chiba-shi 260, Japan*; *a*) To whom inquiries should be addressed.
3) For reviews, see *a*) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N.Y., 1962, pp. 16—18, 108—110; *b*) K.-D. Gundermann, *Angew. Chem.*, 75, 1194 (1963); *c*) B. Capon, *Quart. Revs.*, 18, 45 (1964).
4) S. Ikegami, T. Asai, K. Tsuneoka, S. Matsumura, and S. Akaboshi, *Tetrahedron*, 30, 2087 (1974).
5) For reviews, see *a*) R.D.G. Cooper and D.O. Spry, "Cephalosporins and Penicillins," ed. by E.H. Flynn, Academic Press, New York, N.Y., 1972, pp. 183—254; *b*) T. Kamiya, *J. Soc. Org. Synth. Chem. Japan*, 33, 24 (1975).