The Synthesis and Properties of 2-Substituted Dihydropyrimidines

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Various 2-substituted 1,4-dihydro-4,4,6-trimethyl-1-phenylpyrimidines and 1,6-dihydro-4,6,6-trimethylpyrimidines were synthesized independently. For these dihydropyrimidines, the physical data such as the uv, ir, and nmr spectra and the oxidation potential were compared. 2-Dimethylamino substituted dihydropyrimidine showed the lowest oxidation potential, which expected the similar reducing ability as dihydropyridines.

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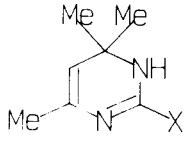
Dihydropyrimidines are interesting compounds from their structures, reactivities, and biological activities as well as aza-analogs of dihydropyridines [1]. In the case of *N*-unsubstituted dihydropyrimidines, the location of the double bonds are ambiguous due to their tautomerism [2]. However, the preferable tautomers depend on the kinds of substituents [3]. Furthermore, we reported that 2-dimethylamino substituted 1,6-dihydropyrimidine alone reacted with acetylenic compounds to yield pyridine derivatives *via* [4 + 2] cycloadducts [4]. In this way, the substituents on the dihydropyrimidine rings influence the properties of dihydropyrimidines. According to previous papers, dihydropyrimidines were synthesized by the desulfurization of pyrimidine-2(1*H*)-thiones and their dihydro derivatives [5]. In this method, however, the substituent of the C-2 carbon on the pyrimidine rings was limited to hydrogen. Herein we describe the preparation of various 2-substituted 1,4-dihydro-4,4,6-trimethyl-1-phenylpyrimidines and 1,6-dihydro-4,6,6-trimethylpyrimidines [6], and the comparison of their properties.



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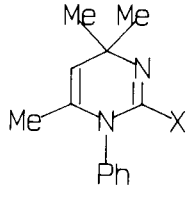

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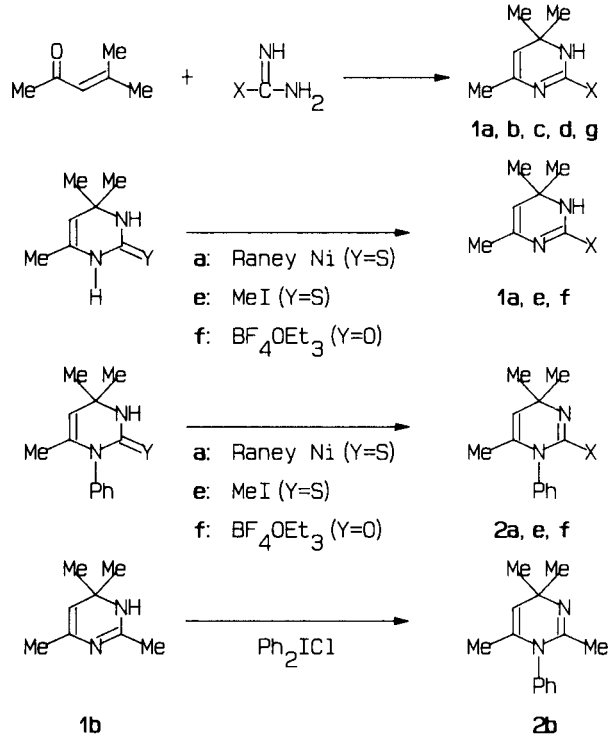
a: X=H b: X=Me c: X=Pr^i

d: X=Ph e: X=SMe f: X=OEt

g: X=NMe_2

Dihydropyrimidines were synthesized by the following three methods. According to the paper of Traube [7], 1,6-dihydro-4,6,6-trimethylpyrimidine derivatives were easily prepared from the condensation of mesityl oxide and amidines or guanidines having various substituents on the C-2 carbons. For example, *N*-unsubstituted dihydropyrimidines having various substituents on the C-2 carbon such as hydrogen (**1a**), methyl (**1b**), isopropyl (**1c**), phenyl (**1d**) [2a], and dimethylamino (**1g**) [2b] were prepared according to this method. However, the corresponding *N*-substituted dihydropyrimidines **2** could not be synthesized by this method. 2-Methylthio (**1e** [8] and **2e** [9]) and 2-ethoxy (**1f** and **2f**) substituted dihydropyrimidines were prepared by the alkylation of 3,4-dihydropyrimidine-2(1*H*)-thiones and pyrimidin-2(1*H*)-ones using methyl iodide and triethyloxonium tetrafluoroborate [10] (Meerwein reagent), respectively. 2-Unsubstituted dihydropyrimidine **2a** was synthesized by the desulfurization of 3,4-dihydropyrimidine-2(1*H*)-thione using Raney nickel [5]. From the corresponding *N*-unsubstituted dihydropyrimidine-2(1*H*)-thione, **1a** was also prepared by this method. *N*-Substituted 2-methyl-1,4-dihydropyrimidine (**2b**) was prepared from the aryla-

Scheme 1



tion of *N*-unsubstituted dihydropyrimidine (**1b**) using diphenyliodonium chloride [11]. In this reaction, the formation of 1,6-dihydropyrimidine isomer was possible. However, this isomer was not detected in the reaction mixture owing to the steric hindrance around the nitrogen atom.

Next, we investigated various properties for these 2-substituted dihydropyrimidines. The various physical data such as the uv, the ir, and the nmr spectra and the oxidation potentials (Ep) were measured and the results are summarized in Table 1. In the uv spectra, 2-phenyldihydropyrimidine showed longer wavelength absorption owing to more conjugated system. On the other hand, 2-ethoxy- and 2-methylthio-1,4-dihydropyrimidine and 2-ethoxy-1,6-dihydropyrimidine absorbed at shorter wavelength than others. In the ir spectra, the characteristic absorption bands in the region of 1600-1700 cm^{-1} were observed. For *N*-substituted 1,4-dihydropyrimidines, characteristic peaks were observed for 1,4-dihydropyrimidines independently of the substituents on the 2-carbon. When the structure of these series was unknown, the ir spectroscopy should be a useful tool for elucidating the structure [12]. Actually, the product which was obtained by the arylation of 1,6-dihydro-2,4,6,6-tetramethylpyrimidine was determined as 1,4-dihydropyrimidine by the ir spectrum at 1680 cm^{-1}, and no absorption band around 1650 cm^{-1} was observed. For *N*-unsubstituted dihydropyrimidines, ir spectroscopy was a good tool for showing that *N*-unsubstituted dihydropyrimidines were mixture of isomers [3a]. In the ^{13}C-nmr spectra, the C-2 carbon in the pyrimidine ring exhibited the characteristic chemical shift for ethoxy (**1f**) and dimethylamino (**1g**) dihydropyrimidines. However, in the ^{1}H- and ^{13}C-nmr spectra, a remarkable difference was not observed at either the C-5 carbons or the H-5 protons, where some difference was observed for three *N*-substituted dihydropyrimidine isomers [5b].

On the contrary, the reducing ability showed the remarkable differences in the various 2-substituted dihydropyridines. Previously, the oxidation potentials of dihydropyrimidines were compared with that of dihydropyridines [5a,13]. Dihydropyrimidines showed higher irreversible oxidation potentials than that of dihydropyridines, which shows that dihydropyrimidines have less reducing abilities. Furthermore, electron withdrawing substituents such as the carbonyl group made higher oxidation potential. When the oxidation potentials were measured for the *N*-unsubstituted dihydropyrimidines using the cyclic voltammetry, irreversible cyclic voltammograms were given in all case. Especially, 2-dimethylaminodihydropyrimidine (**1g**) showed the lowest value in the *N*-unsubstituted dihydropyrimidine systems, and the value is lower than that of 1,4-dihydronicotinamide. The introduction of the dimethylamino group into the dihydropyrimidine ring lowered the oxidation potential.

Consequently, various *N*-substituted and *N*-unsubstituted 2-substituted dihydropyrimidines were prepared independently. When the characteristics was compared, the substituent effects on the C-2 carbon of the pyrimidine ring were observed. Especially, 2-dimethylaminodihydropyrimidine showed lower oxidation potential. It meant that the introduction of dimethylamino group on the dihydropyrimidine rings caused the lowering oxidation potential. Therefore, it was possible that the dihydropyrimidines having dimethylamino group would show the reducing abilities similar to dihydropyridines.

Table 1

The Physical Data of 2-Substituted Dihydropyrimidines

	IR (cm^{-1}) [a] (1600-1700)	^{1}H-NMR [b] (5-H)	^{13}C-NMR (2-C)	^{13}C-NMR (5-C)	UV [c] (λ max)	Ep [d] (V)
1a	1630, 1690	4.35	144.1	106.5	266	0.87
1b	1670, 1690	4.40	152.8	106.1	265	0.80
1c	1640, 1690	4.42	159.9	106.6	275	
1d	1650, 1680	4.56	152.5	106.8	306	0.84
1e	1650, 1690	4.49	153.6	107.6	244	0.85
1f	1640, 1690	4.46	154.3	106.3	269	0.80
1g	1650	4.41	155.0	103.6	267	0.40
2a	1620, 1680	4.47	144.4	106.8	257	1.07
2b	1620, 1680	4.47	149.6	106.6	255	
2e	1670	4.50	150.4	106.6	238	1.12
2f	1630, 1690	4.53	148.7	108.2	237	1.08

[a] Measured in chloroform. [b] δ: Measured in deuteriochloroform. [c] nm: Measured in ethanol. [d] Measured in acetonitrile (*vs.* SCE).

EXPERIMENTAL

Melting points, determined on a Yanagimoto micro melting point apparatus, are uncorrected. Ir spectra were measured on a Jasco IRA-1 infrared spectrophotometer. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Hitachi R-24 and a JEOL-100 spectrometer using tetramethylsilane as an internal standard, respectively. The uv spectra were measured on a Shimadzu UV-365 UV-VIS-NIR recording spectrophotometer. For column chromatography, silica gel (Merck, Kieselgel 60, 230-400 mesh) was used.

Preparation of *N*-Unsubstituted Dihydropyrimidines.

A mixture of mesityl oxide (10 mmoles), amidine or guanidine hydrochloride (10 mmoles), and potassium hydroxide (12 mmoles) in ethanol (30 ml) was refluxed for 3 hours. After filtration of potassium chloride, the solvent was evaporated. The residue was chromatographed on silica gel with hexane-acetone-diethylamine (4:6:1 for **1b** and **1g** or 13:6:1 for **1c**) mixture as eluate, then purified by vacuum distillation.

1,6-Dihydro-2,4,6,6-tetramethylpyrimidine (**1b**).

The compound was obtained in a yield of 53%, bp 125°/2 mm Hg, mp 110.5-112°; ^{1}H-nmr (deuteriochloroform): δ 1.19 (s, 6H), 1.75 (d, 3H, J = 0.7 Hz), 1.94 (s, 3H), 4.40 (q, 1H, J = 0.7 Hz), 6.4 (br s, 1H); ^{13}C-nmr (deuteriochloroform): δ 20.5 (q), 21.5 (q), 32.5 (q), 51.7 (s), 106.1 (d), 134.7 (s), 152.8 (s).

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.26. Found: C, 69.20; H, 10.26; N, 20.18.

1,6-Dihydro-2-isopropyl-4,6,6-trimethylpyrimidine (**1c**).

This product was obtained in a yield of 18% and recrystallized from hexane, mp 100-101°; ^{1}H-nmr (deuteriochloroform): δ 1.15 (d, 3H, J = 7.3 Hz), 1.17 (s, 6H), 1.77 (d, 3H, J = 1.5 Hz), 2.43 (sept, 1H, J = 7.3 Hz), 4.4 (br s, 1H), 4.42 (q, 1H, J = 1.5 Hz); ^{13}C-nmr (deuteriochloroform): δ 20.3 (q), 21.1 (q), 32.1 (q), 34.6 (d), 51.1 (s), 106.6 (d), 135.9 (s), 159.9 (s).

Anal. Calcd. for $C_{10}H_{18}N_2$: C, 72.23; H, 10.91; N, 16.84. Found: C, 72.03; H, 10.97; N, 16.89.

1,6-Dihydro-4,6,6-trimethyl-2-dimethylaminopyrimidine (**1g**).

This compound was obtained in a yield of 64%, mp 87-88° (lit 88-90° [2b]); ^{1}H-nmr (deuteriochloroform): δ 1.20 (s, 6H), 2.16 (d, 3H, J = 1.5 Hz), 3.00 (s, 6H), 4.0 (br s, 1H), 4.41 (q, 1H, J = 1.5 Hz); ^{13}C-nmr (deuteriochloroform): δ 23.1 (q), 31.7 (q), 37.0 (q), 50.7 (s), 103.6 (d), 153.3 (s), 155.0 (s).

1,6-Dihydro-4,6,6-trimethylpyrimidine (**1a**).

A mixture of mesityl oxide (10 mmoles), formamidine acetate (10 mmoles), and potassium hydroxide (12 mmoles) in ethanol (30 ml) was refluxed for 3 hours. After the solvent was evaporated, the residue was chromatographed on silica gel with hexane-acetone-diethylamine (4:6:1) mixture as eluate, then purified by vacuum distillation. This product was obtained in a yield of 21% and recrystallization from hexane, mp 65-66°, bp 33°/10^{-3} mm Hg; ^{1}H-nmr (deuteriochloroform): δ 1.18 (s, 6H), 1.73 (d, 3H, J = 1.0 Hz), 4.35 (q, 1H, J = 1.0 Hz), 5.0 (br s, 1H), 7.00 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 20.1 (q), 32.6 (q), 51.4 (s), 106.5 (d), 133.2 (s), 144.1 (d). This compound was also prepared from the desulfurization of 3,4-dihydro-4,4,6-trimethylpyrimidine-2(1*H*)-thione with Raney nickel [5b] in 49% yield.

Anal. Calcd. for $C_7H_{12}N_2 \cdot 0.05H_2O$: C, 67.20; H, 9.77; N, 22.40. Found: C, 67.11; H, 9.68; N, 22.35.

The Reaction of Dihydropyrimidin-2(1*H*)-ones with the Meerwein Reagent.

To the solution of the Meerwein reagent [10] (4 mmoles) in dichloromethane (10 ml), the solution of dihydropyrimidin-2(1*H*)-one (2 mmoles) in dichloromethane (10 ml) was added dropwise. The mixture was stirred for overnight at room temperature. To the stirred solution was cautiously added a 50% aqueous sodium carbonate solution. The organic layer was dried over anhydrous magnesium sulfate, and evaporated. The residual oil was chromatographed on silica gel with hexane-acetone-diethylamine (25:5:1) mixture as eluate, then purified by vacuum distillation. Picrate was synthesized as follows. To a solution of the dihydropyrimidine (2 mmoles) in ethanol (5 ml) was added a solution of picric acid (2 mmoles) in ethanol (5 ml). After 15 hours the crystalline picrate had precipitated and was filtered off. The product was recrystallized from ethanol.

2-Ethoxy-1,4-dihydro-4,4,6-trimethyl-1-phenylpyrimidine (**2f**).

This product was obtained in a yield of 59%, mp of picrate 134-135°, bp 108°/2 mm Hg; ^{1}H-nmr (deuteriochloroform): δ 1.04 (t, 3H, J = 6.8 Hz), 1.25 (s, 6H), 1.45 (d, 3H, J = 1.5 Hz), 4.04 (q, 2H, J = 6.8 Hz), 4.53 (q, 1H, J = 1.5 Hz), 7.0-7.4 (m, 5H); ^{13}C-nmr (deuteriochloroform): δ 14.2 (q), 19.3 (q), 33.3 (q), 52.4 (s), 61.8 (t), 108.2 (d), 126.9 (d), 128.3 (d), 129.5 (d), 132.5 (s), 139.5 (s), 148.7 (s).

Anal. Calcd. for $C_{21}H_{23}N_5O_8$ (picrate): C, 53.27; H, 4.89; N, 14.79. Found: C, 53.04; H, 4.91; N, 14.68.

2-Ethoxy-1,6-dihydro-4,6,6-trimethylpyrimidine (**1f**).

This product was obtained in a yield of 14% and recrystallized from hexane, mp 41-43°, bp 123°/5 mm Hg; ^{1}H-nmr (deuteriochloroform): δ 1.19 (s, 6H), 1.25 (t, 3H, J = 7.3 Hz), 1.77 (d, 3H, J = 1.0 Hz), 4.17 (q, 2H, J = 7.3 Hz), 4.46 (q, 1H, J = 1.0 Hz), 4.6 (br s, 1H); ^{13}C-nmr (deuteriochloroform): δ 14.5 (q), 28.7 (q), 32.1 (q), 52.9 (s), 61.7 (t), 106.3 (d), 154.0 (s), 154.3 (s).

Anal. Calcd. for $C_9H_{16}N_2O \cdot 0.25H_2O$: C, 62.56; H, 9.65; N, 16.22. Found: C, 62.85; H, 9.38; N, 15.97.

Arylation of *N*-Unsubstituted Dihydropyrimidines.

1,6-Dihydropyrimidine (**1b**, 2 mmoles) was stirred for 1 hour in DMF (10 ml) in the presence of sodium hydride (4 mmoles) on an ice-methanol bath, and then diphenyliodonium chloride [11] (2 mmoles) was added to the mixture. After stirring for 2 hours in an ice-methanol bath, the reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was poured into ice, then dichloromethane added. The organic layer was washed with water, and then dried over magnesium sulfate. After the solvent was evaporated, the crude product was chromatographed on silica gel with a hexane-acetone-diethylamine (13:6:1) mixture as the eluate, then purified by vacuum distillation.

1,4-Dihydro-2,4,4,6-tetramethyl-1-phenylpyrimidine (**2b**).

This product was obtained in a yield of 6%, mp of picrate 158-160°; ^{1}H-nmr (deuteriochloroform): δ 1.26 (s, 6H), 1.43 (d, 3H, J = 1.0 Hz), 1.70 (s, 3H), 4.47 (q, 1H, J = 1.0 Hz), 7.1-7.3 (m, 3H), 7.3-7.5 (m, 2H); ^{13}C-nmr (deuteriochloroform): δ 19.7 (q), 23.1 (q), 32.8 (q), 51.2 (s), 106.6 (d), 127.9 (d), 129.0 (d), 129.9 (d), 131.9 (s), 140.9 (s), 149.6 (s).

Anal. Calcd. for $C_{20}H_{21}N_5O_7$ (picrate): C, 54.17; H, 4.77; N, 15.79. Found: C, 53.95; H, 4.77; N, 15.76.

The other dihydropyrimidines **1d** [2a], **1e** [8], **2a** [5], and **2e** [9] were synthesized by the reported methods.

1,6-Dihydro-4,6,6-trimethyl-2-phenylpyrimidine (**1d**).

This compound was synthesized according to the reported method [2a], mp 95-96° (lit 97-98.5° [2a]); ^{1}H-nmr (deuteriochloroform): δ 1.27 (s, 6H, 1.87 (d, 3H, J = 1.0 Hz), 4.56 (q, 1H, J = 1.0 Hz), 5.1 (br s, 1H), 7.3-7.5 (m, 3H), 7.6-7.8 (m, 2H); ^{13}C-nmr (deuteriochloroform): δ 28.8 (q), 32.3 (q), 51.8 (s), 106.8 (d), 126.4 (d), 128.4 (d), 130.0 (d), 130.4 (s), 135.9 (s), 152.5 (s).

1,6-Dihydro-4,6,6-trimethyl-2-methylthiopyrimidine (**1e**).

This compound was synthesized according to the reported method [8], bp 87°/5 mm Hg; mp 114-115°; ^{1}H-nmr (deuteriochloroform): δ 1.19 (s, 6H), 1.79 (d, 3H, J = 1.5 Hz), 2.42 (s, 3H), 4.49 (q, 1H, J = 1.5 Hz), 4.8 (br s, 1H); ^{13}C-nmr (deuteriochloroform): δ 13.4 (q), 31.5 (q), 32.1 (q), 53.0 (s), 107.6 (d), 153.6 (s), and one carbon.

Anal. Calcd. for $C_8H_{14}N_2S$: C, 56.43; H, 8.29; N, 16.45. Found: C, 56.29; H, 8.43; N, 16.23.

1,4-Dihydro-4,4,6-trimethyl-1-phenylpyrimidine (**2a**).

This compound was synthesized according to our previous papers [5]; ^{1}H-nmr (deuteriochloroform): δ 1.25 (s, 6H), 1.55 (d, 3H, J = 1.2 Hz), 4.47 (q, 1H, J = 1.2 Hz), 7.1-7.5 (m, 6H); ^{13}C-nmr (deuteriochloroform): δ 18.9 (q), 32.7 (q), 52.6 (s), 106.8 (d), 127.1 (d), 127.4 (d), 129.2 (d), 130.9 (s), 140.8 (s), 144.4 (d).

1,4-Dihydro-4,4,6-trimethyl-2-methylthio-1-phenylpyrimidine (**2e**).

This compound was synthesized according to the reported method [9], mp 44-45° (from hexane); ^{1}H-nmr (deuteriochloroform): δ 1.26 (s, 6H), 1.45 (d, 3H, J = 1.0 Hz), 2.24 (s, 3H), 4.50 (q, 1H, J = 1.0 Hz), 7.2-7.5 (m, 5H); ^{13}C-nmr (deuteriochloroform): δ 19.4 (q), 29.0 (q), 32.7 (q), 53.8 (s), 106.6 (d), 128.4 (d), 128.6 (d), 130.9 (d), 132.2 (s), 139.3 (s), and 150.4 (s).

Anal. Calcd. for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37. Found: C, 68.30; H, 7.38; N, 11.34.

Measurement of the Oxidation Potentials (Ep).

A solution of dihydropyrimidine (30 mg) in acetonitrile (30 ml) in the presence of 0.1 *M* tetrabutylammonium perchlorate as the supporting electrolyte was prepared. Cyclic voltammograms [*vs.* saturated calomel reference electrode (SCE)] were obtained on a Hokuto Dendo Potentiostat/Galvanostat Model HA-301, scanning rate 200 mV·sec^{-1}. The oxidation potential (Ep) was calculated from the voltage reading at the maximum electric current.

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[6] Although the structure of *N*-substituted dihydropyrimidines were not determined according to their substituents [2,3], *N*-unsubstituted dihydropyrimidines synthesized in this research were represented as 1,6-dihydropyrimidines.

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