Independent Synthesis of Three Types of *N*-Substituted Dihydropyrimidines by Desulphurization and their Properties [1]

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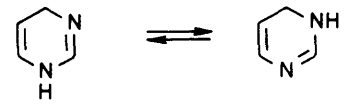
N-Substituted pyrimidine-2(1*H*)-thiones (1), 3,4- (2), and 3,6-dihydropyrimidine-2(1*H*)-thiones (3) were easily desulphurized with Raney nickel to give *N*-substituted 1,2- (4), 1,4- (5), and 1,6-dihydropyrimidines (6), respectively. Further, the properties of these *N*-substituted dihydropyrimidine isomers, *e.g.* spectral characteristics, pK_a values, and stabilities are also discussed.

The synthesis and reactions of *N*-substituted 1,4-dihydropyridines and related compounds have been extensively investigated as model compounds of NAD(P)H.[2,3] It is of interest to study dihydropyrimidines, especially *N*-substituted dihydropyrimidines, because they are aza-analogues of dihydropyridines. It is well known that *N*-unsubstituted dihydropyrimidines exist in tautomeric equilibrium between the form (A) and (B) in solution (Scheme 1). Recently the structures of two tautomers have been assigned by Weis.[4] However, it is impossible to compare directly the properties of the two tautomers because they cannot be isolated in pure form. *N*-Substituted dihydropyrimidines were prepared from the condensation of di-imines and carbonyl compounds,[5] the reductive alkylation of pyrimidines,[6] the cyclization of imidoyl thioamides,[7] and the *N*-methylation of dihydropyrimidines.[8] However, it is quite difficult to synthesize selectively dihydropyrimidines having the same substituents. Furthermore, *N*-substituted 1,4-dihydropyrimidines are hitherto unknown compounds. Therefore, it is expected that the introduction of the substituents on the nitrogen atom would suppress the tautomeric equilibrium and enable us to compare the properties of *N*-substituted dihydropyrimidines which have three possible isomers, *i.e.* the 1,2-, 1,4-, and 1,6-dihydropyrimidine forms.



(A) (B)

Scheme 1.

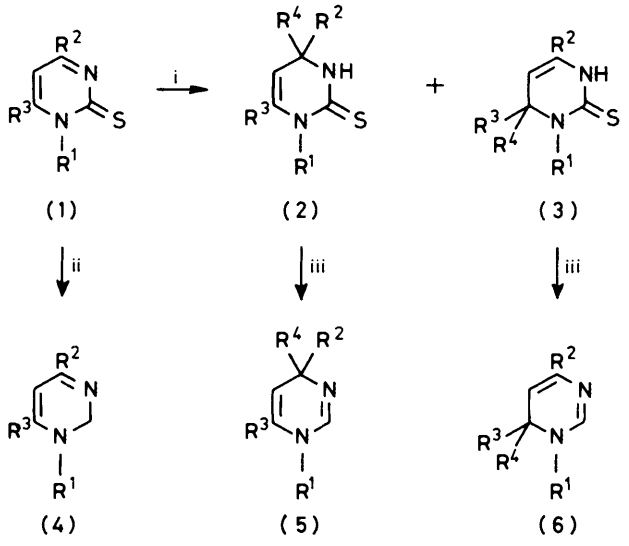
In previous papers we discussed the regioselective synthesis of *N*-substituted 3,4- and 3,6-dihydropyrimidine-2(1*H*)-thiones by the treatment of *N*-substituted pyrimidine-2(1*H*)-thiones with organometallic reagents [9] or metal hydride complexes.[10] Also, Raney nickel has been widely applied to the desulphurization of heterocyclic thiones.[11] We describe herein the independent synthesis of three types of *N*-substituted dihydropyrimidines by the desulphurization of pyrimidine-2(1*H*)-thiones and their dihydro derivatives with Raney nickel. The properties of the *N*-substituted dihydropyrimidine isomers are also discussed.

When 3,4-dihydro-4,6-dimethyl-1-phenylpyrimidine-2(1*H*)-thione (2a) was warmed with Raney nickel in methanol at 50 °C for 1 h, and then refluxed for 2h (Method A), an oily product was obtained which showed a molecular-ion peak at *m/z* 186 in its mass spectrum. The i.r. absorption band at 3 200 cm^{-1} (N–H stretch) of the starting material disappeared. The ^1H n.m.r. spectrum exhibited signals at δ 1.27 (3 H, d, *J* 6.0 Hz), 1.50 (3 H, dd, *J* 1.2 Hz), 4.0—4.3 (1 H, m), and 4.3—4.5 (1 H, m) attributed to 4-Me, 6-Me, 4-H, and an olefinic proton, respectively. The ^{13}C n.m.r. spectrum displayed a new doublet at δ_C 145.8 p.p.m. assignable to C-2 of the pyrimidine ring. On the basis of these data the product was determined to be 1,4-dihydro-4,6-dimethyl-1-phenylpyrimidine (5a) (Scheme 2).

In the same manner, 3,6-dihydro-4,6-dimethyl-1-phenylpyrimidine-2(1*H*)-thione (3a) gave 1,6-dihydro-4,6-dimethyl-1-phenylpyrimidine (6a) which was structurally isomeric with compound (5a). The structure of compound (6d) [obtained similarly from the thione (3d)] was confirmed by comparison of the spectral data with those reported by van der Stoel *et al.*[6]

When 4,6-dimethyl-1-phenylpyrimidine-2(1*H*)-thione (1a) was treated with Raney nickel in the same manner as described above, no desulphurized product was obtained from the reaction mixture. To prevent oxygen influence, the reaction was carried out at room temperature under hydrogen (Method B), and compound (1a) then gave 1,2-dihydro-4,6-dimethyl-1-phenylpyrimidine (4a) in 39% yield. The structure of compound (4a) was determined by the following data. The ^1H n.m.r. spectrum showed a new signal at δ 4.98 (2 H, s) due to the methylene protons at C-2. The ^{13}C n.m.r. spectrum exhibited a new triplet at δ_C 68.3 p.p.m. attributable to C-2 of the pyrimidine ring. Since all three types of *N*-substituted dihydropyrimidine (4)—(6) were very hygroscopic and unstable, the microanalyses were performed on the picrates. The double-bond isomerization in each *N*-substituted dihydropyrimidine isomer (4), (5), and (6) could not be observed under these conditions.

To investigate the characteristic differences of the three isomeric forms we compared the spectral data of the dihydropyrimidine isomers having the same substituents. In the u.v. spectra, compounds (4a) and (6a), which have conjugated double bonds in their pyrimidine rings, have absorption maxima at longer wavelength than those for compound (5a). The i.r. absorption bands in the region 1 600—1 700 cm^{-1} provided an excellent tool for the differentiation of the two isomers in the *N*-unsubstituted dihydropyrimidine series.[4] A similar i.r. tendency is observed for compounds (4a), (5a), and (6a) in the region 1 600—1 700 cm^{-1} where the absorption bands appear at higher frequencies, decreasing in the order (5a) > (6a) > (4a). The olefinic protons at C-5 give ^1H n.m.r. signals at high field in the order (5a) > (6a) > (4a). It was reported that the most important fragmentation process of dihydropyridines in their mass spectra was the formation of the aromatic pyridinium ion.[12] The main fragment peak of compounds (5a) and (6a) was found to be the pyrimidinium cation at *m/z* 171 ($M^+ - 15$), formed by loss of a methyl radical. Further, the pK_a values of the *N*-substituted dihydropyrimidines were measured. The 1,2-dihydropyrimidine (4a) is relatively basic, and the pK_a values of 1,4-dihydropyrimidines depend on the substituents on the phenyl ring at N-1



	R^1	R^2	R^3	R^4
a;	Ph	Me	Me	H
b;	p-MeC_6H_4	Me	Me	H
c;	p-$MeOC_6H_4$	Me	Me	H
d;	Me	Ph	Ph	H
e;	Me	Me	Ph	H
f;	Ph	Me	Me	Me
g;	p-MeC_6H_4	Me	Me	Me
h;	m-MeC_6H_4	Me	Me	Me
i;	p-$MeOC_6H_4$	Me	Me	Me
j;	p-ClC_6H_4	Me	Me	Me
k;	$PhCH_2$	Me	Me	Me

Scheme 2. *Reagents:* i, R^4MgI, R^4Li, $NaBH_4$, or $LiAlH_4$; ii, Raney nickel–H_2–MeOH; iii, Raney nickel–MeOH

of the pyrimidine ring ($\rho = -0.42$). Finally, the stabilities of the 1,4-dihydropyrimidines (5a, f) in solution were measured as the half-lives by means of g.l.c. (Table 1). Compound (5a) is more stable in aprotic solvents than in protic ones. Under acidic conditions, the half-life of (5a) could not be measured by the formation of its salt.

It is concluded that three types of *N*-substituted dihydropyrimidines are independently synthesized by the desulphurization of pyrimidine-2(1*H*)-thiones and their dihydro derivatives with Raney nickel. Further, the properties of *N*-substituted dihydropyrimidines were ascertained by spectral data, pK_a values, and half-lives.

Experimental

M.p.s were measured on a Yanagimoto micro melting point apparatus. I.r. spectra were recorded on a Jasco IRA-1 spectrophotometer. ^1H and ^{13}C N.m.r. spectra were recorded on a Hitachi R-20 and JEOL-100 spectrometer, respectively, using tetramethylsilane as internal standard. U.v. spectra were obtained on a Shimadzu UV-365 UV-VIS-NIR spectrophotometer. Mass spectra were obtained on a Hitachi RMU-6MG spectrometer. G.l.c. was run on a Hitachi 163 Gas Chromatograph using a SE-30 column. pK_a Values were measured on an Iwaki Glass pH/ion meter 225.

Table 1.

Compound	Solvent	Temperature (°C)	Half-life (h) [a]
(5a)	MeOH	50	8.7
(5a)	MeOH	100	2.4
(5a)	MeOH (0.1M-NaOH)	50	17.4
(5a)	C_6H_6	50	18.8
(5f)	MeOH	50	102

[a] Measured by g.l.c.

Materials.—Dihydropyrimidine-2(1*H*)-thiones (2f—k) and (3d) were prepared by the methods of Mathes [13] and Hardtmann,[14] respectively. Compounds (2a—c) and (3a—c) were prepared according to the method described in our previous paper.[10]

3,4-*Dihydro*-4,6-*dimethyl*-1-(p-*tolyl*)*pyrimidine*-2(1H)-*thione* (2b), 42% yield; m.p. 157 °C (decomp.) (from benzene–hexane); $\nu_{max.}$ (KBr) 3 180, 1 680, 1 530, 1 350, 1 215, and 810 cm^{-1}; δ ($CDCl_3$) 1.29 (3 H, d, *J* 6.0 Hz), 1.48 (3 H, dd, *J* 1.2 Hz), 2.35 (3 H, s), 4.0—4.4 (1 H, m), 4.7—4.9 (1 H, m), 7.0—7.4 (4 H, m), and 7.74 (1 H, br s) (Found: C, 67.35; H, 6.95; N, 12.05. $C_{13}H_{16}N_2S$ requires C, 67.20; H, 6.94; N, 12.05%).

3,4-*Dihydro*-1-(p-*methoxyphenyl*)-4,6-*dimethylpyrimidine*-2(1H)-*thione* (2c), 30% yield; m.p. 149 °C (decomp.) (from benzene–hexane); $\nu_{max.}$ (KBr) 3 180, 1 680, 1 505, 1 345, 1 230, 1 215, 1 015, and 810 cm^{-1}; δ ($CDCl_3$) 1.31 (3 H, d, *J* 6.0 Hz), 1.50 (3 H, dd, *J* 1.2 Hz), 3.83 (3 H, s), 4.0—4.4 (1 H, m), 4.7—4.9 (1 H, m), 6.8—7.3 (4 H, m), and 7.60 (1 H, br s) (Found: C, 63.0; H, 6.5; N, 11.2. $C_{13}H_{16}N_2OS$ requires C, 62.87; H, 6.49; N, 11.28%).

3,6-*Dihydro*-4,6-*dimethyl*-1-(p-*tolyl*)*pyrimidine*-2(1H)-*thione* (3b), 82% yield; m.p. 191—192 °C (from ethyl acetate); $\nu_{max.}$ (KBr) 3 180, 1 700, 1 505, 1 460, 1 430, 1 245, 805, 770, and 710 cm^{-1}; δ ($CDCl_3$) 1.20 (3 H, d, *J* 6.0 Hz), 1.80 (3 H, dd, *J* 1.0 Hz), 2.36 (3 H, s), 4.0—4.4 (1 H, m), 4.6—4.9 (1 H, m), 7.0—7.4 (4 H, m), and 8.60 (1 H, br s) (Found: C, 67.1; H, 6.95; N, 11.95. $C_{13}H_{16}N_2S$ requires C, 67.20; H, 6.94; N, 12.05%).

3,6-*Dihydro*-1-(p-*methoxyphenyl*)-4,6-*dimethylpyrimidine*-2(1H)-*thione* (3c), 97% yield; m.p. 185—188 °C (from ethyl acetate); $\nu_{max.}$ (KBr) 3 180, 1 700, 1 600, 1 500, 1 460, 1 430, 1 230, 1 020, and 815 cm^{-1}; δ ($CDCl_3$) 1.20 (3 H, d, *J* 6.0 Hz), 1.80 (3 H, dd, *J* 1.0 Hz), 3.82 (3 H, s), 4.1—4.5 (1 H, m), 4.6—4.9 (1 H, m), 6.8—7.3 (4 H, m), and 8.53 (1 H, br s) (Found: C, 62.7; H, 6.45; N, 11.25. $C_{13}H_{16}N_2OS$ requires C, 62.87; H, 6.49; N, 11.28%).

3,6-*Dihydro*-1-*methyl*-4,6-*diphenylpyrimidine*-2(1H)-*thione* (3d), 100% yield; m.p. 167—168.5 °C (from benzene); $\nu_{max.}$ (KBr) 3 200, 1 670, 1 520, 1 475, 1 270, 1 120, 740, and 680 cm^{-1}; δ ($CDCl_3$) 3.27 (3 H, s), 5.12 (2 H, s), and 7.33 (10 H, s) (Found: C, 72.75; H, 5.75; N, 10.0. $C_{17}H_{16}N_2S$ requires C, 72.82; H, 5.75; N, 9.99%).

Preparation of Raney Nickel.—Sodium hydroxide pellets (5 g) were added to a vigorously stirred solution of nickel–aluminium alloy (Wako Pure Chemical Industries Ltd; *ca.* 50%; 4 g) in distilled water (60 ml) at room temperature. After 15 min the reaction mixture was immersed in an oil-bath (bath temperature 70 °C) for 20 min, and then the alkaline solution was decanted. The nickel was washed several times by suspension in distilled water and decantation. The washing procedure was repeated several times with methanol.

Desulphurization of Pyrimidinethiones.—(a) *Method A.* A mixture of 3,4-dihydro-4,6-dimethyl-1-phenylpyrimidine-

2(1*H*)-thione (2a) (5 mmol) and Raney nickel (2 g) in methanol (20 ml) was warmed at 50 °C for 1 h and then refluxed for 2 h. After removal of the catalyst by filtration the filtrate was diluted with water and extracted with dichloromethane; the extract was dried over anhydrous magnesium sulphate. The crude product was chromatographed on silica gel with hexane–acetone–diethylamine (13 : 6 : 1) as eluant to give 1,4-*dihydro*-4,6-*dimethyl*-1-*phenylpyrimidine* (5a), $\nu_{max.}$ (liquid film) 1 680, 1 620, 1 590, 1 490, 1 280, 1 160, 755, and 690 cm^{-1}; δ_H ($CDCl_3$) 1.27 (3 H, d, *J* 6.0 Hz), 1.50 (3 H, dd, *J* 1.2 Hz), 4.0—4.3 (1 H, m), 4.3—4.5 (1 H, m, 5-H), and 7.0—7.5 (6 H, m); δ_C ($CDCl_3$) 18.9 (q), 25.4 (q), 50.0 (d), 102.6 (s), 127.1 (d), 127.3 (d), 129.2 (d), 132.5 (s), 140.8 (s), and 145.8 p.p.m. (d); $\lambda_{max.}$ (log ε) (EtOH) 258 nm (3.77); *m/z* 186 (M^+), 185, 183, 172, 171 (M^+ − 15, 100%), 117, and 77; pK_a 8.43.

In this way were similarly prepared 1,4-*dihydro*-4,6-*dimethyl*-1-(p-*tolyl*)*pyrimidine* (5b), $\nu_{max.}$ (liquid film) 1 700, 1 625, 1 610, 1 510, 1 365, 1 290, 1 175, 910, and 815 cm^{-1}; δ ($CDCl_3$) 1.27 (3 H, d, *J* 6.0 Hz), 1.50 (3 H, dd, *J* 1.2 Hz), 2.35 (3 H, s), 4.0—4.3 (1 H, m), 4.3—4.5 (1 H, m, 5-H), and 6.9—7.3 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 255 nm (3.78).

1,4-*Dihydro*-1-(p-*methoxyphenyl*)-4,6-*dimethylpyrimidine* (5c), $\nu_{max.}$ (liquid film) 1 690, 1 620, 1 510, 1 285, 1 245, 1 165, 1 105, 1 030, 900, and 825 cm^{-1}; δ ($CDCl_3$) 1.27 (3 H, d, *J* 6.0 Hz), 1.47 (3 H, dd, *J* 1.2 Hz), 3.77 (3 H, s), 4.0—4.3 (1 H, m), 4.3—4.5 (1 H, m, 5-H), and 6.7—7.2 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 250 nm (3.60).

1,4-*Dihydro*-4,4,6-*trimethyl*-1-*phenylpyrimidine* (5f), $\nu_{max.}$ (liquid film) 1 680, 1 590, 1 490, and 760 cm^{-1}; δ_H ($CDCl_3$) 1.25 (6 H, s), 1.55 (3 H, d, *J* 1.2 Hz), 4.47 (1 H, q, *J* 1.2 Hz, 5-H), and 7.1—7.5 (6 H, m); δ_C ($CDCl_3$) 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), and 144.4 p.p.m. (d); $\lambda_{max.}$ (log ε) (EtOH) 257 nm (3.82); *m/z* 200 (M^+), 186, 185 (M^+ − 15, 100%), and 118; pK_a 8.57.

1,4-*Dihydro*-4,4,6-*trimethyl*-1-(p-*tolyl*)*pyrimidine* (5g), $\nu_{max.}$ (liquid film) 1 690, 1 630, 1 605, 1 515, 1 485, 1 440, 1 400, 1 365, 1 285, 1 115, 1 025, 910, 840, and 815 cm^{-1}; δ ($CDCl_3$) 1.25 (6 H, s), 1.52 (3 H, d, *J* 1.2 Hz), 2.33 (3 H, s), 4.34 (1 H, q, *J* 1.2 Hz, 5-H), and 7.0—7.3 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 255 nm (3.86); *m/z* 214 (M^+), 200, and 199 (M^+ − 15, 100%); pK_a 8.63.

1,4-*Dihydro*-4,4,6-*trimethyl*-1-(m-*tolyl*)*pyrimidine* (5h), $\nu_{max.}$ (liquid film) 1 685, 1 605, 1 585, 1 490, 1 335, 1 305, 1 260, 1 185, 905, 845, and 700 cm^{-1}; δ ($CDCl_3$) 1.24 (6 H, s), 1.57 (3 H, d, *J* 1.2 Hz), 2.37 (3 H, s), 4.46 (1 H, q, *J* 1.2 Hz, 5-H), and 6.8—7.5 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 257 nm (3.71); pK_a 8.54.

1,4-*Dihydro*-1-(p-*methoxyphenyl*)-4,4,6-*trimethylpyrimidine* (5i), $\nu_{max.}$ (liquid film) 1 685, 1 620, 1 505, 1 335, 1 240, 1 030, 905, and 825 cm^{-1}; δ ($CDCl_3$) 1.24 (6 H, s), 1.56 (3 H, d, *J* 1.2 Hz), 3.80 (3 H, s), 4.40 (1 H, q, *J* 1.2 Hz, 5-H), and 6.7—7.2 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 251 nm (3.91); *m/z* 230 (M^+), 216, 215 (M^+ − 15, 100%), and 200; pK_a 8.68.

1-(p-*Chlorophenyl*)-1,4-*dihydro*-4,4,6-*trimethylpyrimidine* (5j); $\nu_{max.}$ (liquid film) 1 680, 1 610, 1 595, 1 485, 1 335, 1 465, 1 180, 1 095, 1 020, and 820 cm^{-1}; δ ($CDCl_3$) 1.24 (6 H, s), 1.53 (3 H, d, *J* 1.2 Hz), 4.47 (1 H, q, *J* 1.2 Hz, 5-H), and 6.9—7.5 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 265 nm (3.82); pK_a 8.68.

1-*Benzyl*-1,4-*dihydro*-4,4,6-*trimethylpyrimidine* (5k), $\nu_{max.}$ (liquid film) 1 680, 1 605, 1 335, 1 205, 1 165, 960, 815, and 685 cm^{-1}; δ ($CDCl_3$) 1.20 (6 H, s), 1.52 (3 H, d, *J* 1.2 Hz), 4.33 (1 H, q, *J* 1.2 Hz, 5-H), 4.45 (2 H, s), 6.98 (1 H, s), and 7.2—7.4 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 254 nm (3.49).

1,6-*Dihydro*-4,6-*dimethyl*-1-*phenylpyrimidine* (6a), $\nu_{max.}$ (liquid film) 1 650, 1 560, 1 490, 1 360, 1 270, and 1 170 cm^{-1}; δ_H ($CDCl_3$) 1.23 (3 H, d, *J* 6.0 Hz), 1.87 (3 H, dd, *J* 1.0 Hz), 4.5—4.8 (1 H, m), 4.8—5.0 (1 H, m, 5-H), and 7.1—7.5 (6 H, m); δ_C ($CDCl_3$) 22.0 (q), 22.1 (q), 51.0 (d), 106.2 (d), 120.2 (d), 124.9 (d), 129.6 (d), 140.2 (s), 142.7 (s), and 146.2 p.p.m. (d); $\lambda_{max.}$ (log ε) (EtOH) 311 nm (3.72); *m/z* 186 (M^+), 172, 171 (M^+ − 15, 100%), and 104; pK_a 8.40.

1,6-*Dihydro*-4,6-*dimethyl*-1-(p-*tolyl*)*pyrimidine* (6b), $\nu_{max.}$ (liquid film) 1 650, 1 570, 1 515, 1 375, 1 280, 1 180, 1 125, and 915 cm^{-1}; δ ($CDCl_3$) 1.20 (3 H, d, *J* 6.0 Hz), 1.83 (3 H, dd, *J* 0.6 and 1.2 Hz), 2.32 (3 H, s), 4.3—4.7 (1 H, m), 4.7—5.0 (1 H, m, 5-H), and 6.9—7.3 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 310 nm (3.67).

1,6-*Dihydro*-1-(p-*methoxyphenyl*)-4,6-*dimethylpyrimidine* (6c), $\nu_{max.}$ (liquid film) 1 650, 1 580, 1 515, 1 370, 1 250, 1 190, 1 035, and 830 cm^{-1}; δ ($CDCl_3$) 1.17 (3 H, d, *J* 6.0 Hz), 1.82 (3 H, dd, *J* 1.0 Hz), 3.77 (3 H, s), 4.3—4.7 (1 H, m), 4.7—4.9 (1 H, m, 5-H), and 6.7—7.3 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 302 nm (3.57).

1,6-*Dihydro*-1-*methyl*-4,6-*diphenylpyrimidine* (6d) had properties in accord with those in the literature.[6]

(b) *Method B.* A mixture of 4,6-dimethyl-1-phenylpyrimidine-2(1*H*)-thione (1a) (5 mmol) and Raney nickel (3 g) in methanol (20 ml) was stirred at room temperature for 3 h under hydrogen. After removal of the catalyst by filtration, the filtrate was worked up according to Method A. The crude product was chromatographed on silica gel with hexane–acetone–diethylamine (26 : 12 : 1 or 6 : 6 : 1) as eluant to give 1,2-*dihydro*-4,6-*dimethyl*-1-*phenylpyrimidine* (4a), $\nu_{max.}$ (liquid film) 1 610, 1 590, 1 530, and 855 cm^{-1}; δ_H ($CDCl_3$) 1.83 (3 H, d, *J* 0.6 Hz), 2.20 (3 H, dd, *J* 0.6 Hz), 4.98 (2 H, s), 5.37 (1 H, s, 5-H), and 7.1—7.5 (5 H, m); δ_C ($CDCl_3$) 18.5 (q), 22.9 (q), 68.3 (t), 101.4 (d), 125.1 (d), 125.3 (d), 128.5 (d), 142.7 (s), 150.0 (s), and 164.5 p.p.m. (s); $\lambda_{max.}$ (log ε) (EtOH) 343 nm (3.86); pK_a 9.66.

In this way were similarly prepared 1,2-*dihydro*-4,6-*dimethyl*-1-(p-*tolyl*)*pyrimidine* (4b), $\nu_{max.}$ (liquid film) 1 620, 1 515, 1 425, 1 265, 1 215, 905, and 730 cm^{-1}; δ ($CDCl_3$) 1.81 (3 H, d, *J* 0.3 Hz), 2.01 (3 H, dd, *J* 1.0 Hz), 2.33 (3 H, s), 4.93 (2 H, s), 5.30 (1 H, s, 5-H), and 6.9—7.4 (4 H, m); $\lambda_{max.}$ (log ε) (EtOH) 343 nm (3.71).

1,2-*Dihydro*-1-(p-*methoxyphenyl*)-4,6-*dimethylpyrimidine* (4c), $\nu_{max.}$ (liquid film) 1 615, 1 510, 1 245, 1 135, 1 035, 905, and 835 cm^{-1}; δ ($CDCl_3$) 1.76 (3 H, d, *J* 0.6 Hz), 1.98 (3 H, dd, *J* 0.6 Hz), 3.77 (3 H, s), 4.87 (2 H, s), 5.27 (1 H, s, 5-H), and 6.7—7.2 (4 H, m); $\lambda_{max.}$ (log ε) (EtOH) 343 nm (3.68).

1,2-*Dihydro*-1,4-*dimethyl*-6-*phenylpyrimidine* (4e), $\nu_{max.}$ (liquid film) 1 605, 1 530, 1 285, 1 195, 750, and 690 cm^{-1}; δ ($CDCl_3$) 2.03 (3 H, dd, *J* 1.0 Hz), 2.72 (3 H, s), 4.70 (2 H, s), 5.47 (1 H, s, 5-H), and 7.2—7.6 (5 H, m); $\lambda_{max.}$ (log ε) (EtOH) 355 nm (3.59).

Yields are summarized in Table 2.

Preparation of the Dihydropyrimidine Picrates.—To a solution of the dihydropyrimidine (2 mmol) in ethanol (5 ml) was added a solution of picric acid (2 mmol) in ethanol (5 ml). After 15 h the crystalline picrate had precipitated and was filtered off. The product was recrystallized from ethanol. Analytical data are summarized in Table 2.

Measurements of the pK_a *Values.*—The compound (0.3 mmol) and sulphamic acid (0.4 mmol) were dissolved in 50% aqueous ethanol. The pH of the solution was measured after every addition of 0.1ml during titration with 0.06M-sodium hydroxide. The pK_a was calculated from each pH reading.

Measurements of the Stabilities.—Compound (5a) or (5f) (0.25 mmol) was dissolved in methanol or benzene (1 ml). The solution was divided into a number of sealed tubes and each was heated. The decreasing amount of 1,4-dihydropyrimidine

Table 2. Yields and analytical data of dihydropyrimidines

Reactant	Method [a]	Product	Yield (%)	M.p. (°C) [b]	Analysis (%) [b] Found (Required) C	H	N	Formula
(1a)	B	(4a)	39	127—128	52.28 (52.05	4.04 4.12	16.99 16.86)	$C_{18}H_{17}N_5O_7$
(1b)	B	(4b)	36	134—135	53.27 (53.14	4.38 4.46	16.28 16.31)	$C_{19}H_{19}N_5O_7$
(1c)	B	(4c)	35	119—120	51.36 (51.23	4.25 4.30	15.80 15.72)	$C_{19}H_{19}N_5O_8$
(1e)	B	(4e)	66	166	52.32 (52.05	4.08 4.12	16.85 16.86)	$C_{18}H_{17}N_5O_7$
(2a)	A	(5a)	54	155—156	52.18 (52.05	4.05 4.12	16.73 16.86)	$C_{18}H_{17}N_5O_7$
(2b)	A	(5b)	57	133—134	53.14 (53.14	4.43 4.46	16.11 16.31)	$C_{19}H_{19}N_5O_7$
(2c)	A	(5c)	71	114—115	51.19 (51.23	4.29 4.30	15.65 15.72)	$C_{19}H_{19}N_5O_8$
(2f)	A	(5f)	81	145—147	53.33 (53.14	4.45 4.46	16.37 16.31)	$C_{19}H_{19}N_5O_7$
(2g)	A	(5g)	82	159—161	54.42 (54.17	4.74 4.77	15.97 15.79)	$C_{20}H_{21}N_5O_7$
(2h)	A	(5h)	78	171	53.93 (54.17	4.74 4.77	15.57 15.79)	$C_{20}H_{21}N_5O_7$
(2i)	A	(5i)	84	119—120	52.41 (52.28	4.55 4.60	15.35 15.24)	$C_{20}H_{21}N_5O_8$
(2j)	A	(5j)	81	120—121	49.44 (49.20	3.93 3.91	15.07 15.05)	$C_{19}H_{18}ClN_5O_7$
(2k)	A	(5k)	83	105—106	53.87 (54.17	4.72 4.77	15.73 15.79)	$C_{20}H_{21}N_5O_7$
(3a)	A	(6a)	74	131—132	52.26 (52.05	4.10 4.12	16.73 16.86)	$C_{18}H_{17}N_5O_7$
(3b)	A	(6b)	49	155—156	53.20 (53.14	4.39 4.46	16.38 16.31)	$C_{19}H_{19}N_5O_7$
(3c)	A	(6c)	43	123—124	51.30 (51.23	4.30 4.30	15.70 15.72)	$C_{19}H_{19}N_5O_8$
(3d)	A	(6d) [c]	27					

[a] See Experimental section. [b] Of picrate. [c] Known compound (see ref. 6).

was determined at appropriate intervals by g.l.c. with biphenyl as internal standard. The results are summarized in Table 1.

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