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INDEPENDENT SYNTHESIS OF THREE TYPES OF N-SUBSTITUTED DIHYDROPYRIMIDINES AND THEIR REACTIONS WITH MALACHITE GREEN

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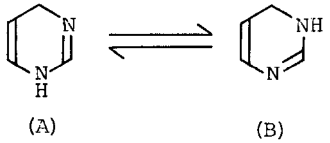
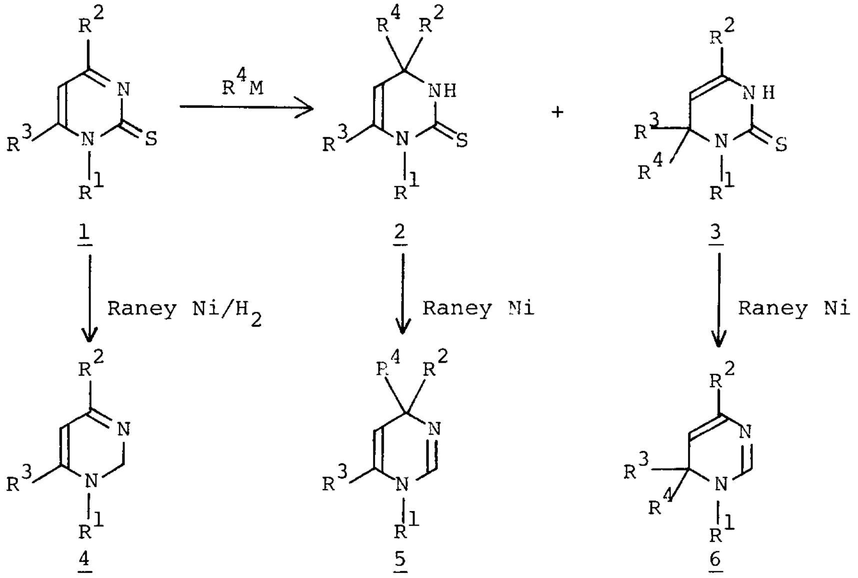
Summary: Pyrimidine-2(1H)-thiones and their corresponding dihydro-derivatives were treated with Raney nickel to afford respectively three types of dihydropyrimidine isomers, which reacted with malachite green in similar rate constants to 1-benzyl-1,4-dihydronicotinamide.

The synthesis and reactions of N-substituted 1,4-dihydropyridines and their derivatives have been extensively investigated as model compounds of NAD(P)H[1]. However, little attention has been paid to the synthesis and properties of dihydropyrimidines, especially N-substituted pyrimidines, in spite of the fact that they are aza-analogs of dihydropyridines[2]. N-Unsubstituted dihydropyrimidines exist in solution in tautomeric equilibrium between A and B[3] (Scheme I). It is, therefore, expected that this equilibrium is suppressed by introduction of substituents on nitrogen atom. We previously reported that N-substituted 3,4- and 3,6-dihydropyrimidine-2(1H)-thiones were selectively obtained from the corresponding pyrimidine-2(1H)-thiones with organometallic reagents or metal hydride complexes[4]. Also, Raney nickel has been widely applied to the desulfurization of thiocarbonyls on heterocycles[5]. In this paper, the independent synthesis of N-substituted dihydropyrimidine isomers by desulfurization with Raney nickel is described. The chemical behaviors of dihydropyrimidines are also compared with those of 1-benzyl-1,4-dihydronicotinamide (BNAH).



Scheme I

3,4-Dihydropyrimidine-2(1H)-thiones (2, 5 mmol) were warmed with Raney nickel (2 g) in methanol (20 ml) at 50 °C for 1 h, then refluxed for 2 h to afford 1,4-dihydropyrimidines (5)[6] (Method A). By similar treatment of 3,6-dihydropyrimidine-2(1H)-thiones (3) with Raney nickel, 1,6-dihydropyrimidines (6) were obtained[7]. On the other hand, pyrimidine-2(1H)-thiones (1) were treated with Raney nickel for 3 h at room temperature under hydrogen atmosphere to give 1,2-dihydropyrimidines (4)[8] (Method B). The spectroscopic characteristics for three types of dihydropyrimidines are summarized in Table I. Under these conditions, the double bond isomerization in each isomer 4, 5, and 6 could not be observed.



$R^4M = R^4MgI,\ R^4Li,\ NaBH_4,\ \text{or}\ LiAlH_4$

a; R^1=Ph, R^2=R^3=Me, R^4=H   b; R^1=p-MeC_6H_4, R^2=R^3=Me, R^4=H

c; R^1=p-$MeOC_6H_4$, R^2=R^3=Me, R^4=H   d; R^1=Me, R^2=R^3=Ph, R^4=H

e; R^1=CH_2Ph, R^2=R^3=R^4=Me   f; R^1=Ph, R^2=R^3=R^4=Me

Scheme II

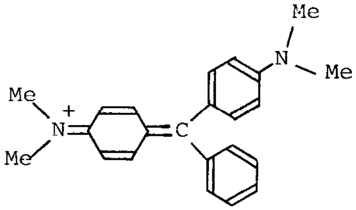
Table I

Reactant	Method	Product	Yield (%)	mp. (°C) (as picrate)	IR (cm^{-1})	NMR (δ, 5-H)	UV (nm) (λ_{max}^{EtOH})	Ep (V) (vs. SCE)
1a	B	4a	39	127-128	1610	5.67	343	0.812
1b	B	4b	36	134-135	1620	5.43	343	0.800
1c	B	4c	35	119-120	1615	5.27	343	0.730
2a	A	5a	54	155-156	1680	4.40	258	0.992
2b	A	5b	57	133-134	1700	4.40	255	0.974
2c	A	5c	71	114-115	1690	4.40	250	0.969
2e	A	5e	83	105-106	1685	4.45	254	1.042
2f	A	5f	81	145-147	1680	4.47	257	1.070
3a	A	6a	74	131-132	1650	4.90	311	1.011
3b	A	6b	49	155-156	1670	4.85	310	1.006
3c	A	6c	43	123-124	1650	4.80	302	0.974

Since dihydropyridines act as the reducing agents, the oxidation potential (Ep) of each dihydropyrimidine isomer in acetonitrile was measured by cyclic voltammetry in the presence of 0.1 M tetrabutylammonium perchlorate as the supporting electrolyte (see Table I). The oxidation potentials showed somewhat higher values than BNAH (Ep=0.700 V). Further, the oxidation potentials changed by the substituents on nitrogen atom. From the fact that BNAH reacts with malachite green to afford leucomalachite green[9], malachite green was treated with 4a, 5a, and 6a in ethanol. The product was found to be leucomalachite green, which was identified by LPC with an authentic sample. On the assumption that the reaction proceeds in second order, the rate constant was evaluated by the decrease of the absorbance of malachite green (λ_{max}=622 nm), and the results are summarized in Table II. It is noteworthy that compound 5f, which has no hydrogen at C-4 position of pyrimidine ring, reacted with malachite green in nearly equal rate constant to compound 5a. The rate constant for reaction with malachite green was also evaluated by changing the solvent. The reaction is apparently promoted in protic solvents. Further, no correlation between the rate constant and the

Table II
Rate Constant (k) for the Reaction with Malachite Green in Ethanol

Reactant	log k (M^{-1} min^{-1})
4a	3.02
5a	3.16
5f	3.18
6a	3.02
BNAH	3.11



Malachite Green

Table III
Solvent Effect of Rate Constant (k)

Solvent	Dielectric Const.[a]	log k (M^{-1} min^{-1})	
		5f	BNAH
MeOH	32.70	3.60	3.57
EtOH	24.55	3.18	3.11
i-PrOH	19.92	2.40	2.81
t-BuOH	12.47	2.28	2.95
MeCN	37.5	<0.84	1.80
$CHCl_2CHCl_2$	8.20	<0.86	<1.18
H_2O-MeCN (1:1)	———	2.16	2.17
D_2O-MeCN (1:1)	———	2.39	2.62

a) J. A. Riddick and W. B. Bunger, 'Organic Solvents,' Wiley-Interscience, New York, 1970.

dielectric constant of solvents is observed (see Table III).

It is concluded that the independent synthesis of three types of dihydropyrimidine isomers is established by the desulfurization of pyrimidine-2(1H)-thiones and the corresponding dihydro-derivatives. Furthermore, these dihydropyrimidines react with malachite green to give leucomalachite green similarly to BNAH. The study on mechanism is now in progress; the details will be reported elsewhere.

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6) For 5a : IR (ν_{max}, neat) 1680, 1620, 1590, 1490, 1280, 1160, 755, and 690 cm^{-1}; NMR (δ, $CDCl_3$) 1.27 (3H, d, J=6.0 Hz), 1.50 (3H, dd, J=1.2 Hz), 4.0-4.3 (1H, m), 4.3-4.5 (1H, m), and 7.0-7.5 ppm (6H, m); (as picrate found: C, 52.18; H, 4.05; N, 16.73. $C_{18}H_{17}N_5O_7$ requires C, 52.05; H, 4.12; N, 16.86 %).

7) The structure of product 6d was comfirmed by comparison of spectral data with those reported by van der Stoel et al.[2c].

8) For 4a : IR (ν_{max}, neat) 1610, 1590, 1530, and 855 cm^{-1}; NMR (δ, $CDCl_3$) 1.83 (3H, d, J=0.6 Hz), 2.20 (3H, dd, J=0.6 Hz), 4.98 (2H, s), 5.37 (1H, s), and 7.1-7.5 ppm (6H, m); (as picrate found: C, 52.28; H, 4.04; N, 16.99. $C_{18}H_{17}N_5O_7$ requires C, 52.05; H, 4.12; N, 16.86 %).

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