# STUDIES ON THE PROPERTIES AND REACTIONS OF 1-ARYL-2(1H)-PYRIMIDINONES

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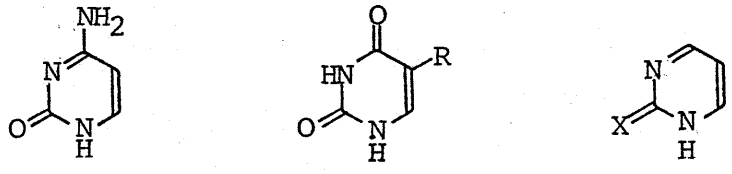
CONTENTS

# I INTRODUCTION

Hydrogen bonds between nucleic acid bases play an important role in the double helical structure of DNA. The bases are classified into purines and pyrimidines. Purine bases consist of adenine and guanine. Pyrimidine bases consist of cytosine, uracil, and thymine which are regarded as 4-amino-, 4-hydroxy-5-methyl-2(1H)-pyrimidinone, respectively. (Fig. 1) 2(1H)-Pyrimidinones, therefore, are considered to be the parent nuclei of the biologically important pyrimidine bases.

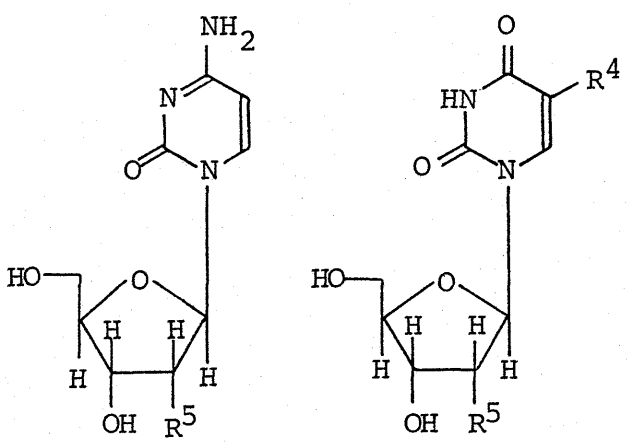


Cytosine R=H Uracil X=O 2(1H)-Pyrimidinone

R=Me Thymine X=S 2(1H)-Pyrimidinethione

Fig. 1

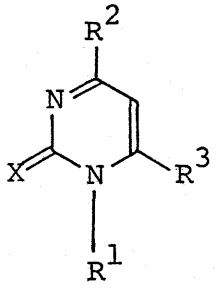
Especially, 1-substituted 2(1H)-pyrimidinones are considered to be analogous compounds for nucleosides, because nucleosides have substituent groups such as D-ribosyl or 2-deoxy-D-ribosyl group on N-1 position of nucleic acid bases. (Fig. 2) From the points of view, it seems to be very important to investigate the properties and reactivities of 1-substituted 2(1H)-pyrimidinones and their derivatives.




$R^5$=H or OH

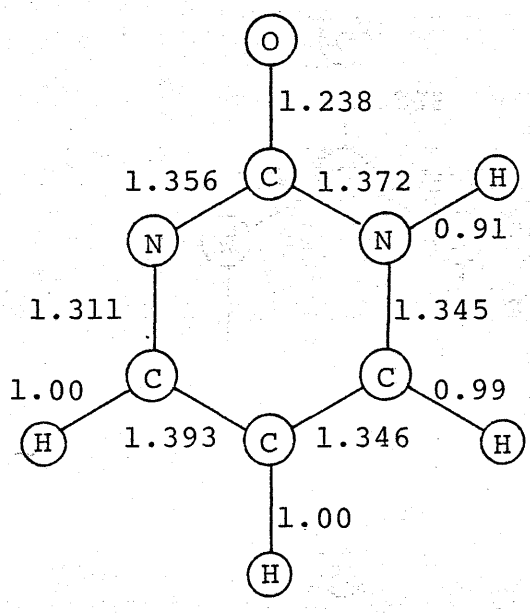
Cytidine $R^4$=H Uridine

$R^4$=Me Thymidine

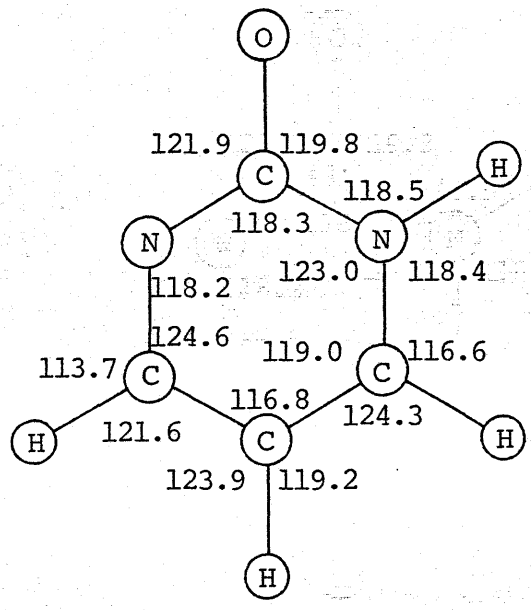



X = O or S

Fig. 2




Bond Length (Å)

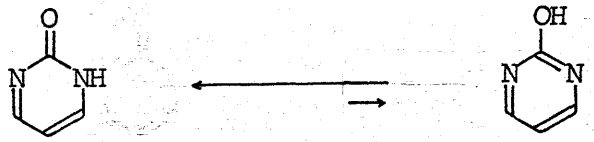



Bond Angle (°)

Fig. 3

2(1H)-Pyrimidinone (1) is an unsaturated six membered ring compound containing four ring carbons, two ring nitrogens and a carbonyl group. The structure of 1 has been confirmed by X-ray crystallographic method[1),2)]. (Fig. 3)

The nature of the potentially tautomeric forms in 1-unsubstituted 2(1H)-pyrimidinone (1) has been studied by means of UV and IR spectroscopy, and X-ray crystallographic analysis. 2(1H)-Pyrimidinone exists predominantly in lactam (keto) form (1a) both in solution and in crystalline state[3)-6)]. (Scheme 1)



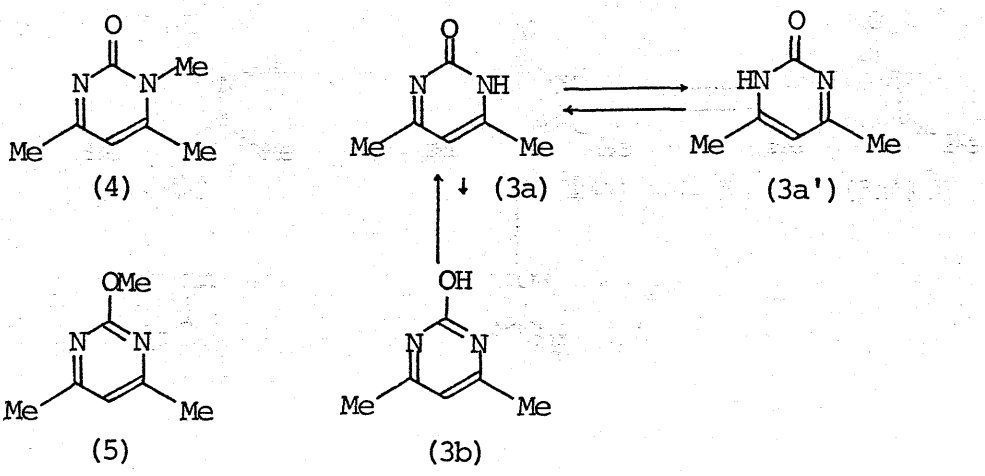
(1a) (1b)

| | Lactam(Keto) form | | Lactim(Enol) form |
|---|---|---|---|
| in $CCl_4$ | 100 | : | 1 |
| in $H_2O$ | 2200 | : | 1 |

Scheme 1

The tautomerism of 4,6-dimethyl-2(1H)-pyrimidinone (3) has also been investigated by the comparison of PMR and CMR spectral data of 1,4,6-trimethyl-2(1H)-pyrimidinone (4) and 2-methoxy-4,6-dimethylpyrimidine (5) which are the fixed model compounds of each tautomeric form[7)]. (Scheme 2)
In the case of 4,6-dimethyl-2(1H)-pyrimidinone (3), the predominant form is a lactam (3a) as in the case of compound 1, because the chemical shifts of H-5 and C-5 carbon of 3 are very similar to those of compound 4. Two signals of C-4 and

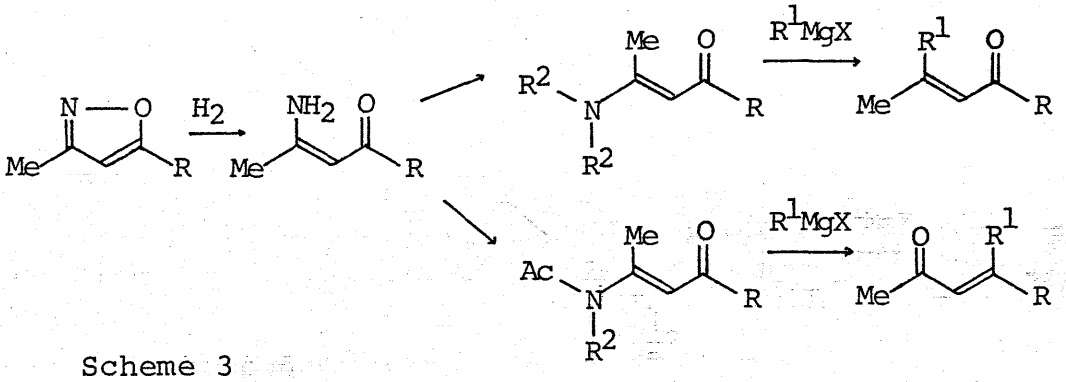
C-6 carbon of compound 3 are very similar to those of compound 4. Two signals of C-4 and C-6 carbon of compound 3 coalesce into broad singlet at room temperature. From these facts, it is ascertained that compound 3a is in tautomeric equilibrium with 3a' by proton transfer between N-1 and N-3 nitrogen. Since it is very difficult to differentiate C-4 and C-6 carbon chemically, the control of the reaction sites of 1-unsubstituted 2(1H)-pyrimidinones is impossible for the attack of nucleophiles or electrophiles. On the contrary, two signals of C-4 and C-6 carbon of compound 4 are observed as singlets, respectively. Therefore, 1-substituent groups are quite necessary to study the regioselective reactions of 2(1H)-pyrimidinones.




Scheme 2

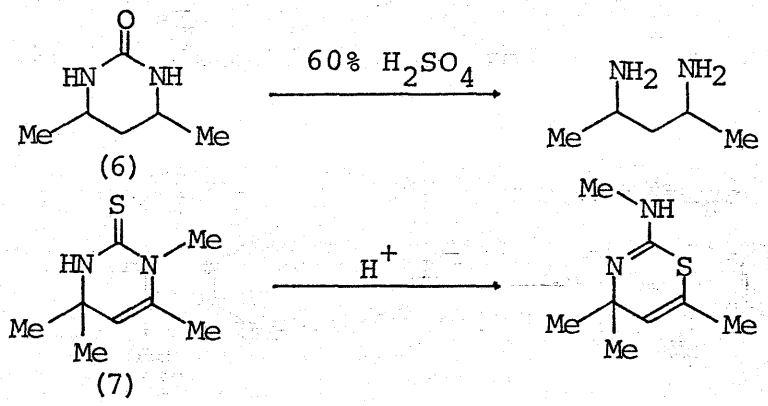
For convenience, 1-substituted 2(1H)-pyrimidinones, which have different substituents at C-4 and C-6 position in the pyrimidine ring, are called "unsymmetrical" 2(1H)-pyrimidinones.

Recently, heterocyclic compounds have been paid attention for the useful synthetic intermediates[8),9)]. For example, isoxazoles are converted into isomeric enones selectively by using catalytic hydrogenation, dialkylation or acylation, and Grignard reaction[10)]. (Scheme 3)



Scheme 3

Also, a few synthetic reactions using 2(1H)-pyrimidinones have been reported. 4,6-Dimethyl-2(1H)-pyrimidinone (6) is hydrolyzed with 60% sulfuric acid to give 2,4-diaminopentane[11)]. 3,4-Dihydro-1,4,4,6-tetramethyl-2(1H)-pyrimidinethione (7) is transformed into 2-methylamino-4,4,6-trimethyl-4H-1,3-thiazine by the action of acids[12)]. (Scheme 4)



Scheme 4

Therefore, the author is interested in the investigation of the utility of 2(1H)-pyrimidinones as synthetic intermediates.

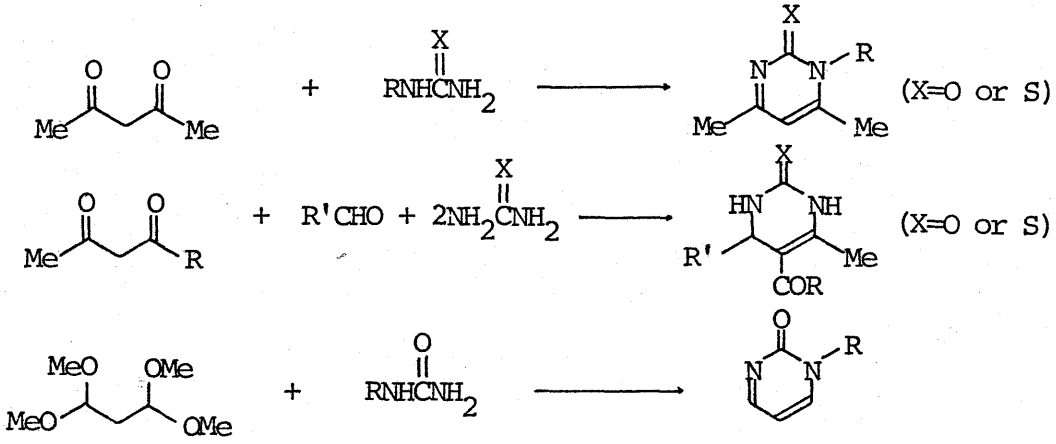
It is well known that biphenyl compounds exist in two rotational isomers by the restricted rotation around central carbon-carbon single bond[13]. Actually, optically active two rotational isomers of 6,6'-dinitrophenoic acid are isolated by the optical resolution method[14]. (Fig. 4)

Fig. 4

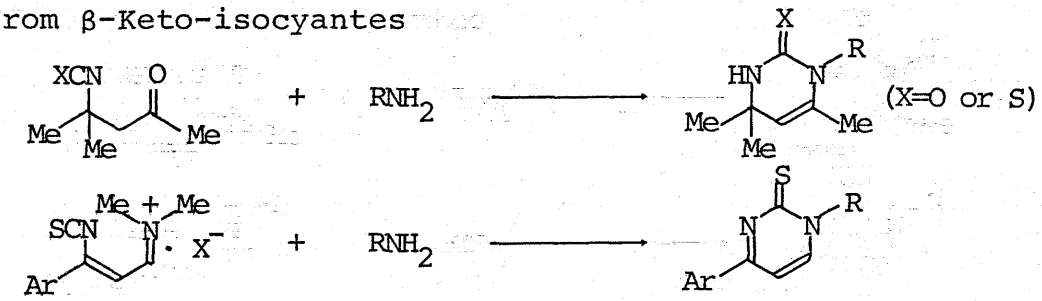
Since 1-aryl-2(1H)-pyrimidinones are considered to be aza-analogues of biphenyl compounds, it is expected that two rotational isomers exist by the restricted rotation around the carbon-nitrogen single bond. Thus, the activation parameters and rotational barriers around the carbon-nitrogen single bond will be revealed by the optical resolution of two rotational isomers.

Many papers have been reported on the preparation of 2(1H)-pyrimidinones. There are mainly four types of preparative methods. (Scheme 5) The first method is the condensation of β-diketones with ureas[15)-26)], and this method has been widely used because of easily available starting materials. The second method is the addition of primary amines to β-keto-isocyanates and isothiocyanates[27)-36)], and this method is

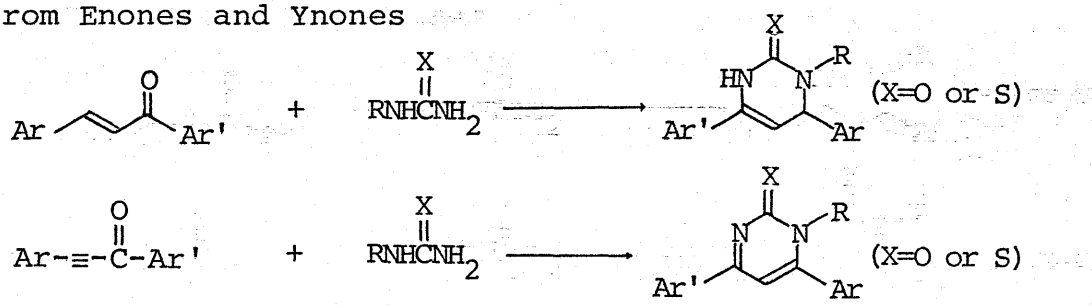
1. From β-Diketones



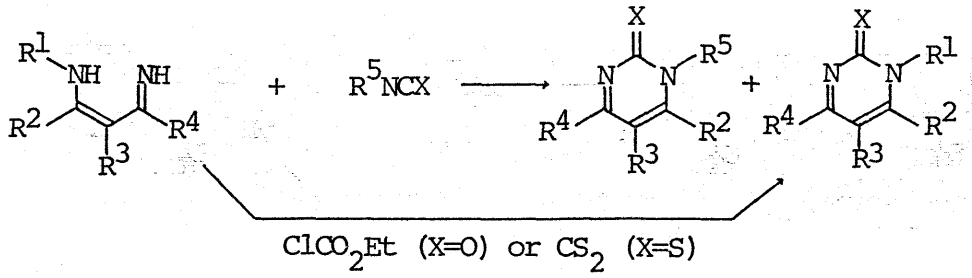

2. From β-Keto-isocyantes




3. From Enones and Ynones

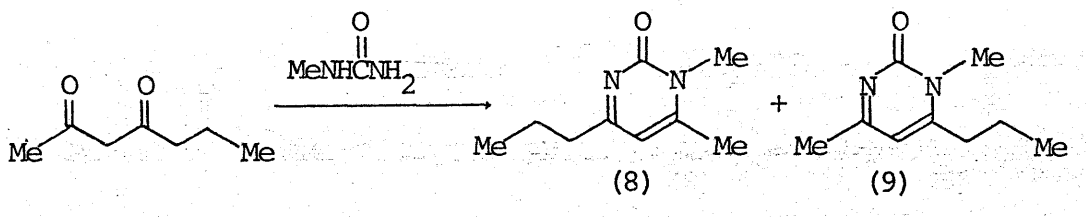



4. From 1,3-Diimines




Scheme 5

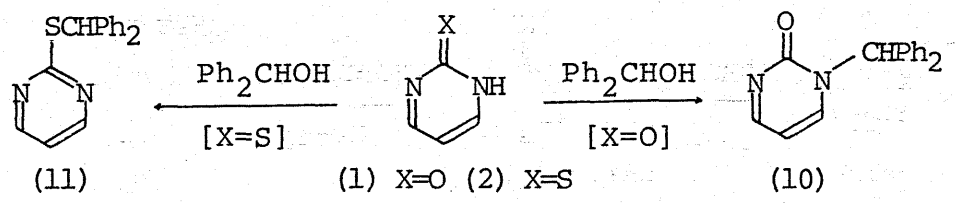
particularly useful for the preparation of dihydro-2(1H)-pyrimidinones. The third method is the Michael addition of ureas to enones or ynones[37)-51)]. This reaction proceeds in good yields in the case of only diaryl substituted compounds such as chalcone or benzoyl phenylacetylene. The fourth method is the reaction of 1,3-diimines with ethyl chloroformate, carbon disulfide[52)] or heterocumulenes[53)]. Further, 2(1H)-pyrimidinones have been supplied from the reaction of ureas with diamines[54),55)], γ-pyrones[56),57)] and 3-ethoxy-2-methoxy-methlenepropionnitrile[58),59)], the thermal rearrangement of 2-alkoxypyrimidines[60)]. Although the great majority of synthetic works on 2(1H)-pyrimidinones has dealt with 1-unsubstituted compounds, some of these methods are applicable for 1-substituted 2(1H)-pyrimidinones. In the first method, two isomeric mixtures of unsymmetrical 2(1H)-pyrimidinones are obtained. However, it is very difficult to separate these two isomers. Heptane-2,4-dione, for example, is treated with N-methylurea to give the mixure of 1,6-dimethyl-4-propyl- (8) and 1,4-dimethyl-6-propyl-2(1H)-pyrimidinone (9)[61)]. (Scheme 6)




Scheme 6

In the third method, unsymmetrical 2(1H)-pyrimidinones are obtained selectively. However, the starting materials in this method are sometimes commercially unobtainable. After all, there is no general method for the regioselective preparation of unsymmetrical 2(1H)-pyrimidinones.

2(1H)-Pyrimidinones have many reaction sites for electrophiles and nucleophiles. 2(1H)-Pyrimidinones react with alkyl halides[62)-64)], acetic anhydride[58),59),65)] or alkyl esters of p-toluene sulfonic acid[66),67)] to give N-alkyl or N-acetyl derivatives. On the other hand, 2(1H)-pyrimidinethiones afford S-alkyl or S-acetyl derivatives[46)-48),68)]. 2(1H)-Pyrimidinone (1) reacts with diphenylcarbinol in acetic acid to give 1-diphenylmethyl-2(1H)-pyrimidinone (10), while 2(1H)-pyrimidinethione (2) affords 2-[(diphenylmethyl)thio]-pyrimidine (11)[69)]. (Scheme 7)

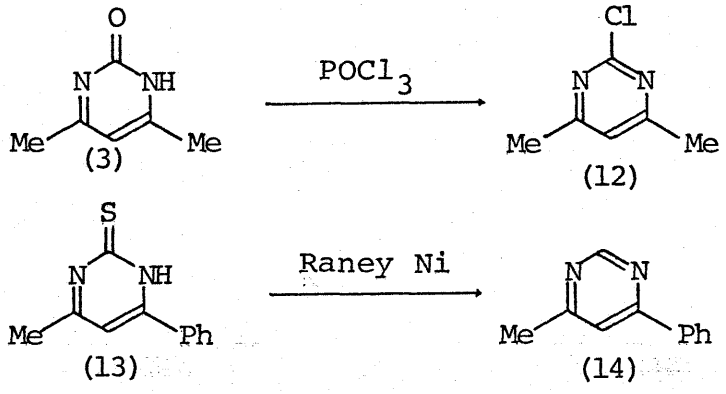



(11) (1) X=O (2) X=S (10)

Scheme 7

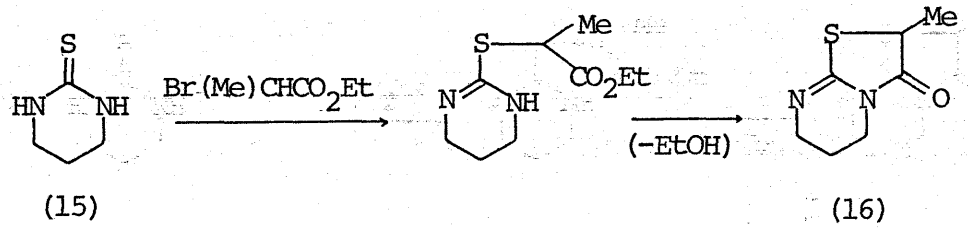
From the fact that 4,6-dimethyl-2(1H)-pyrimidinone (3) is treated with phosphorus oxychloride to yield 2-chloro-4,6-dimethylpyrimidine (12), and 2(1H)-pyrimidinethione is inert to this reagent, chlorination is characteristic reaction in 2(1H)-pyrimidinones. (Scheme 8) On the other hand, desulfuration is characteristic reaction in 2(1H)-pyrimidine-

thiones. 4-Methyl-6-phenyl-2(1H)-pyrimidinethione (13) is treated with Raney nickel to afford 4-methyl-6-phenylpyrimidine (14)[70),71)]. (Scheme 8)



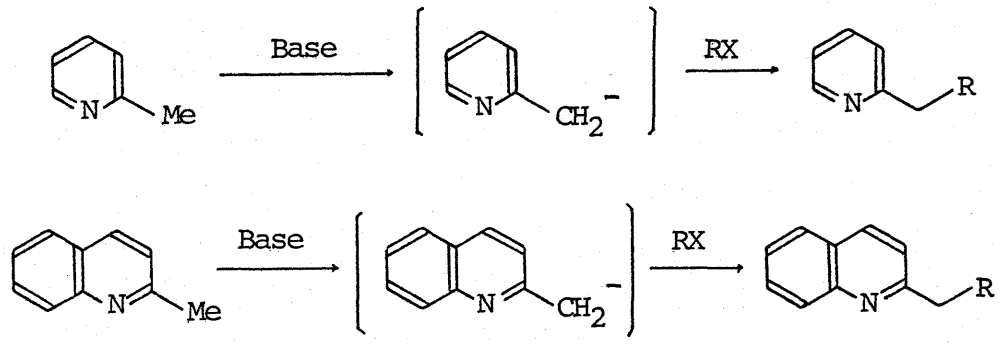

Scheme 8

Using this characteristic reaction, tetrahydro-2(1H)-pyrimidinethione (15) reacts with ethyl α-bromopropionate in the presence of base to yield ring fused product (16)[72)]. (Scheme 9) The similar ring formation reactions have also been reported[74)-76),83)].



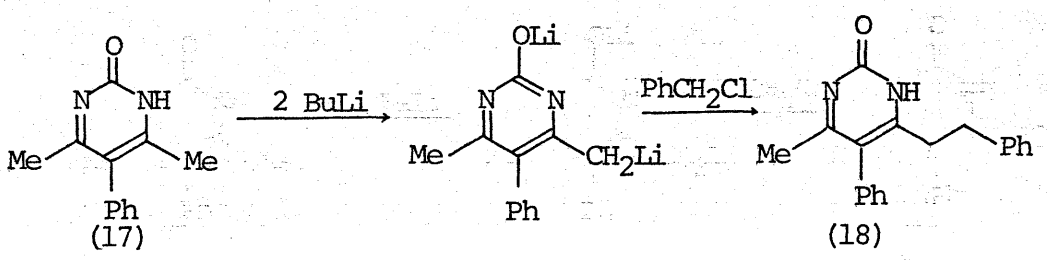

Scheme 9

It is well known that methyl protons are easily activated by the adjacent aromatic ring, especially nitrogen containing heteroaromatic ring. For example, methyl protons of 2-methylpyridine[77)] or 2-methylquinoline[78)] are easily deprotonated by base to give carbanion, which reacts with electrophiles to give substitution products on the methyl group. (Scheme 10)




Scheme 10

Since methyl protons at C-4 and C-6 position are activated by electron-withdrawing effect of the two ring nitrogens, the similar substitution reaction with electrophiles can be expected on methyl groups of 2(1H)-pyrimidinones. Treatment of 4,6-dimethyl-5-phenyl-2(1H)-pyrimidinone (17) with two molecular equivalents of n-butyl lithium and subsequent trapping with benzyl chloride afford 4-methyl-5-phenyl-6-phenetyl-2(1H)-pyrimidinone (18)[79),80)]. (Scheme 11)

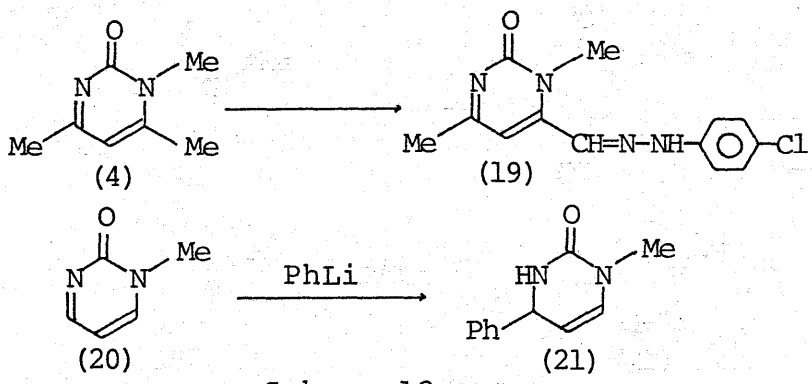



Scheme 11

The Mannich reaction[73)], Aldol type condensations[81)-84)] and diazo-coupling on methyl groups of 2(1H)-pyrimidinones have also been reported. The nitration and bromination in acidic conditions at C-5 position of 2(1H)-pyrimidinones have been extensively studied by Fox[86)] and Tee[87)-90)], respectively.

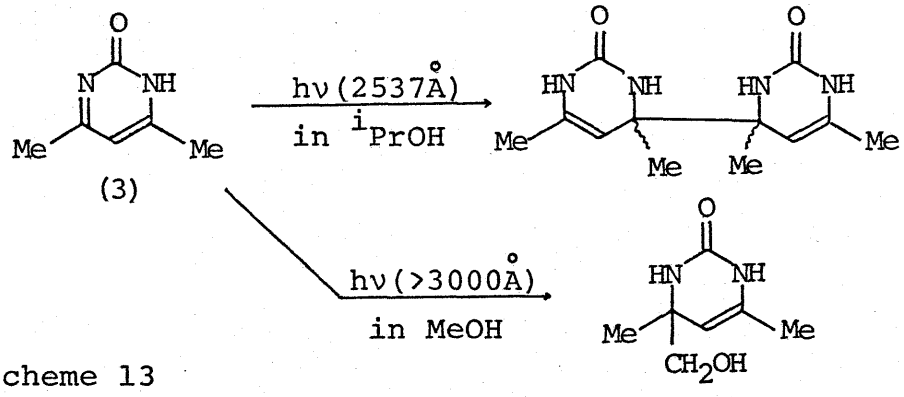
The reaction of 1-unsubstituted 2(1H)-pyrimidinones with electrophiles have been extensively investigated, while a few papers have been reported on the reaction of 2(1H)-pyrimidinones with nucleophiles.

In addition, few papers concerning the chemical behaviors of 1-substituted 2(1H)-pyrimidinones have been reported. 1,4,6-Trimethyl-2(1H)-pyrimidinone (4) undergoes the diazo-coupling with p-chlorobenzenediazonium chloride to give p-chlorophenylhydrazone (19) selectively[85]. 1-Methyl-2(1H)-pyrimidinone (20) is treated with phenyl-lithium to afford 3,4-dihydro-1-methyl-4-phenyl-2(1H)-pyrimidinone (21)[91)-93)]. (Scheme 12)



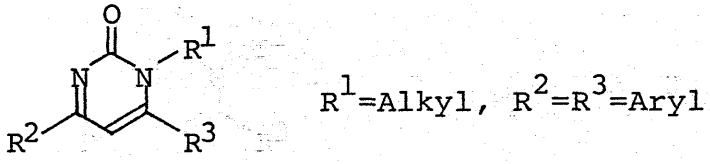

Scheme 12

The photochemistry of nucleic bases and their related compounds is a significant area for understanding the photo-reactivity and the photo-mutation of nucleic acids, and this area has been widely studied[94)-96)]. However, little attention has been paid to the photochemical reaction of 2(1H)-pyrimidinones. The only one photochemical reaction of 2(1H)-pyrimidinones have been reported by Pfoertner[97)], to the best of a knowledge. (Scheme 13)



Scheme 13

A reseach of pharmaceutical activities is one of the most important fields in drug chemistry. Various pharmaceutical activities on 1-unsubstituted or 1-alkyl-2(1H)-pyrimidinones have been examined. 1-Alkyl-4,6-diaryl-2(1H)-pyrimidinones, for example, exhibit the tranquilizing and sedative activity[41),42),49),50),66)]. (Scheme 14)



Scheme 14

On the contrary, the pharmaceutical activity of 1-aryl-2(1H)-pyrimidinones has not been reported. Thus, it seems to be interesting to examine the pharmaceutical activity of 1-aryl-2(1H)-pyrimidinones.

After all, many interests such as the unsymmetrical preparation, the nucleophilic reaction and the synthetic utility of 1-substituted 2(1H)-pyrimidinones have been revealed. In these situations, the author feels much importance to

investigate the properties and reactions of 1-substituted 2(1H)-pyrimidinones. In the case of 1-aryl-2(1H)-pyrimidinones, the restricted rotation around the carbon-nitrogen single bond can be expected. Furthermore, 1-aryl-2(1H)-pyrimidinones are superior to the corresponding 1-alkyl derivatives in the point of easier handling and purification.

In this thesis, the author would like to describe the properties and reactions of 1-aryl-2(1H)-pyrimidinones, especially

(1) The general preparative method of unsymmetrical 1-aryl-2(1H)-pyrimidinones.

(2) The elucidation of the restricted rotation around the carbon-nitrogen single bond.

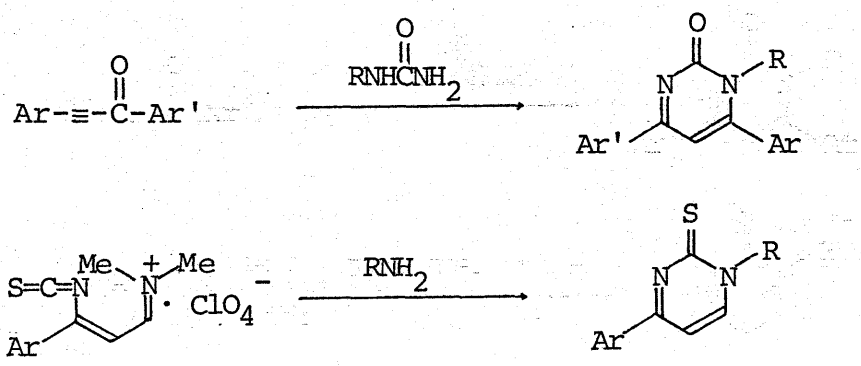
(3) The reaction of 1-aryl-2(1H)-pyrimidinones with various nucleophilic reagents.

(4) The extensive utility of 1-aryl-2(1H)-pyrimidinones as synthetic intermediates.

## RESULTS AND DISCUSSION

### II THE PREPARATIONS AND PROPERTIES

Recently a number of papers on the chemistry of 2(1H)-pyrimidinones have been reported. (See INTRODUCTION) The great majority of synthetic works on 2(1H)-pyrimidinones has been concerned with 1-unsubstituted or 1-alkyl compounds, whereas few papers have been reported on 1-aryl-2(1H)-pyrimidinones. Further, in the very limited cases, the preparation of unsymmetrical 1-substituted 2(1H)-pyrimidinones has been attempted. By the reaction of ynones with amines[49] or 3-isothiocyanato-2-propeniminium perchlorates with amines[36], unsymmetrical 2(1H)-pyrimidinones are obtained. (Scheme 15)



Scheme 15

However, these starting materials are sometimes available with some difficulties. After all, there is no general method for the selective preparation of unsymmetrical 1-substituted 2(1H)-pyrimidinones. Therefore, the author investigated the selective preparation of unsymmetrical 1-aryl-2(1H)-pyrimi-

dinones.

To the best of a knowledge, there is no report on the IR spectra of 1-aryl-2(1H)-pyrimidinones. The UV spectra of the only 1,4-diaryl-2(1H)-pyrimidinethiones have been reported by Liebscher[36]. Although there have been some reports on the PMR spectra[53),98)] of 1-aryl-2(1H)-pyrimidinones, the CMR spectra have been reported only in the case of 5-alkyl-1-phenyl-2(1H)-pyrimidinethiones[98)]. Therefore, the author investigated the spectra of 1-aryl-2(1H)-pyrimidinones for elucidating their structures.

Many papers[13),96)-106)] have been reported on the optical resolution of rotational isomers of biphenyl compounds caused by the restricted rotation around the carbon-nitrogen single bond, since the first example about the optical resolution of 6,6'-dinitrophenoic acid was reported by Christie[14)]. On the other hand, few papers concerning the restricted rotation around the carbon-nitrogen single bond have been reported[107)]. In 1931, Bock and Adams succeeded in separating the enantiomers of 1-(2-carboxyphenyl)-2,5-dimethylpyrrole-3-carboxylic acid by the formation of the brucine salts[108),109)]. (Fig. 5) This is the first example for the optical resolution caused by the restricted rotation around the carbon-nitrogen single bond. Recently, the barriers to hindered rotation around the N-glycosidic single bond were determined by dynamic PMR and CMR spectroscopy, and found to be in the range 10-17 kcal $mol^{-1}$ 110)-112)]. Since

1-aryl-2(1H)-pyrimidinones were considered to be aza-analogues of biphenyl compounds, the author investigated the structure and rotational isomerism around the carbon-nitrogen single bond.

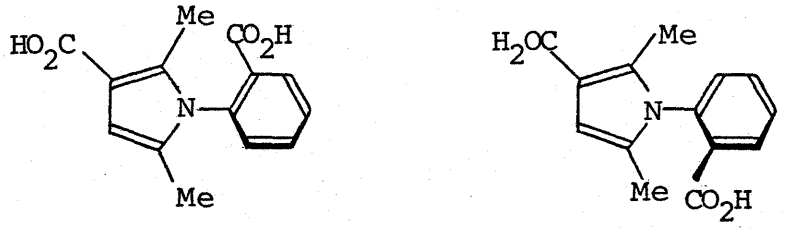



Fig. 5

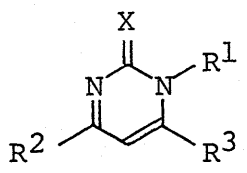
Among the properties of heterocyclic compounds, the research of the pharmaceutical activity is one of the most important fields. The pharmaceutical activities concerning 1-unsubstituted and 1-alkyl-2(1H)-pyrimidinones have been tested. 1-Alkyl-4,6-diaryl-2(1H)-pyrimidinones exhibit the tranqulizing and sedative activity[41),49),66)]. As an extensive study of 1-substituted 2(1H)-pyrimidinones, the author tested the antiinflammatory activity of 1-aryl-2(1H)-pyrimidinones.

## II-1 The Preparations

### II-1-1 The Preparation from β-Diketones[113)]

Many papers have been reported on the synthesis of 1-unsubstituted 2(1H)-pyrimidinones. On the other hand, few papers concerning the synthesis of 1-substituted derivatives have been reported. In order to investigate the properties and reactions, 1-substituted 2(1H)-pyrimidinones were prepared as follows. (Fig. 6) Compounds 4 and 22 were prepared by the method of Hale[16),17)]. Compound 20 was prepared by the method of Fox[26)]. Compounds 23-27 were prepared according to the method of Brown[114)]. Compounds 28-53 were prepared by the modification of Hutchins's method[11)]. New 1-aryl-2(1H)-pyrimidinones were listed in Table 1.

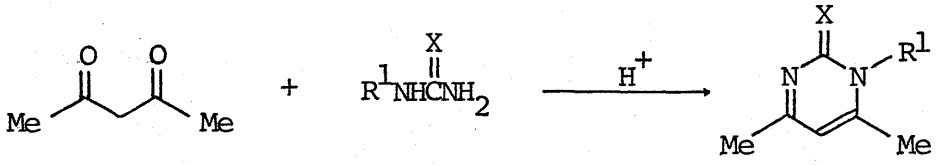
The nucleophiles such as Grignard reagents[115)] attack regioselectively at the β-carbon of β-aminoenones, which are isoelectronic with the enol form of β-diketones. On the reaction of β-diketones with ureas as nucleophiles, the product ratio of unsymmetrical isomers depends upon the structure of the enol form and the nucleophilicities of two nitrogens of ureas[61)]. Benzoylacetone is predominantly tautomerized to be 1-phenyl-1-hydroxy-1-buten-3-one. Moreover, comparing the nucleophilicities of anilines and ammonia, more nucleophilic nitrogen of N-phenylurea and -thiourea



| Compd. No | X | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|
| 4 | O | Me | Me | Me |
| 20 | O | Me | H | H |
| 22 | S | Me | Me | Me |
| 23 | O | Ph | H | H |
| 24 | O | p-$MeC_6H_4$ | H | H |
| 25 | O | p-$MeOC_6H_4$ | H | H |
| 26 | O | o-$MeC_6H_4$ | H | H |
| 27 | S | Ph | H | H |
| 28 | O | Me | Ph | Me |
| 29 | S | Me | Me | Ph |
| 30 | O | Me | Ph | Ph |
| 31 | O | p-$MeC_6H_4$ | Ph | Ph |
| 32 | O | Ph | Me | Me |
| 33 | O | p-$MeC_6H_4$ | Me | Me |
| 34 | O | p-$MeOC_6H_4$ | Me | Me |
| 35 | O | p-$ClC_6H_4$ | Me | Me |
| 36 | S | Ph | Me | Me |
| 37 | S | p-$MeC_6H_4$ | Me | Me |

Fig. 6

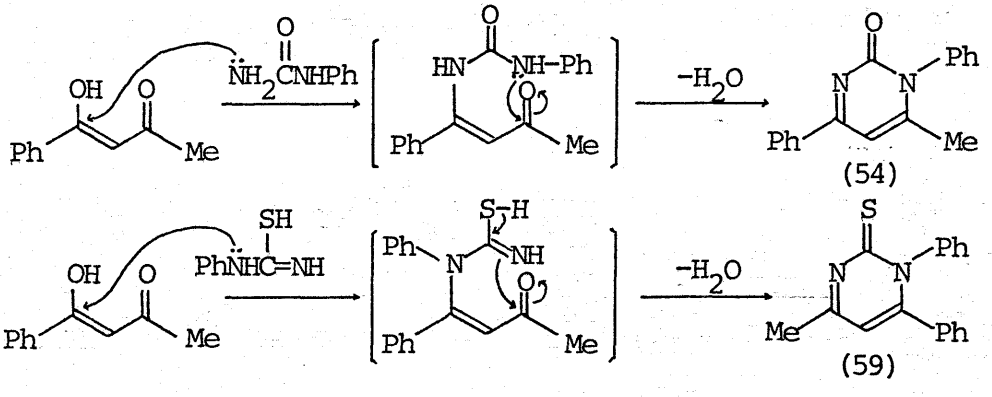
Table 1



| Compd. No | X | $R^1$ | Method[a] | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|
| 38 | O | m-$MeC_6H_4$ | A | 215-216 | 74 |
| 39 | O | m-$MeOC_6H_4$ | A | 195 | 42 |
| 40 | O | o-$MeC_6H_4$ | B | 132-133 | 21 |
| 41 | O | o-$MeOC_6H_4$ | B | 186-187 | 14 |
| 42 | O | o-$EtC_6H_4$ | B | 133 | 21 |
| 43 | O | o-$EtOC_6H_4$ | B | 122-124 | 11 |
| 44 | O | o-$FC_6H_4$ | B | 141-142 | 12 |
| 45 | O | o-$ClC_6H_4$ | B | 103-105 | 12 |
| 46 | O | o-$BrC_6H_4$ | B | 157-158 | 12 |
| 47 | O | β-Naphthyl | B | 197-198 | 17 |
| 48 | S | o-$MeC_6H_4$ | A | 197[b] | 87 |
| 49 | S | o-$MeOC_6H_4$ | A | 163[b] | 86 |
| 50 | S | o-$EtC_6H_4$ | A | 196[b] | 85 |
| 51 | S | o-$EtOC_6H_4$ | A | 142[b] | 86 |
| 52 | S | o-$ClC_6H_4$ | A | 139[b] | 83 |
| 53 | S | o-Me-m-$ClC_6H_3$ | A | 191[b] | 55 |

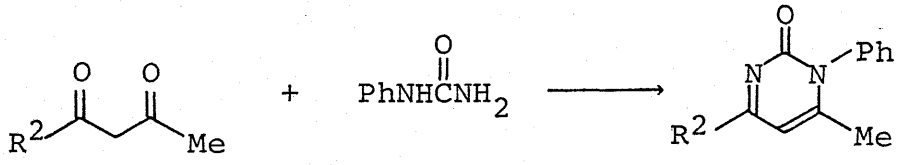
a) See experimental section. b) Decomposition.

prefers to attack at the β-carbon. Therefore, the reaction of benzoylacetone with N-phenylurea and -thiourea was attempted. When benzoylacetone reacted with N-phenylurea in the presence of hydrochloric acid, two products, 6-methyl-1,4-diphenyl-2(1H)-pyrimidinone (54) and 4-methyl-1,6-diphenyl-2(1H)-pyrimidinone (55) were obtained. The yield of 54 was 34%, while that of 55 was only 4%. On the contrary, the reaction of benzoylacetone with N-phenylthiourea afforded 4-methyl-1,6-diphenyl-2(1H)-pyrimidinethione (59) in 82% yield without the isomeric 6-methyl-1,4-diphenyl-2(1H)-pyrimidinethione (71). Similarly the reaction of other benzoylacetone derivatives with N-phenylurea and -thiourea was carried out, and the results were shown in Table 2 and 3. It is known that the alkylation of ureas occurs on nitrogens to afford N-alkylated products, while that of thioureas occurs on sulfur to give S-alkylated products. On the basis of this fact, the reaction mechanism is speculated as follows. (Scheme 16)




Scheme 16

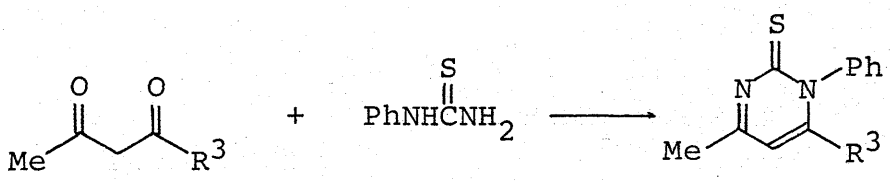
Table 2



| Compd. No | $R^2$ | Method[a] | Mp[b] (°C) | Yield (%) |
|---|---|---|---|---|
| 54 | Ph | A | 222 | 34 |
| 56 | p-$MeC_6H_4$ | A | 259 | 23 |
| 57 | p-$MeOC_6H_4$ | A | 254 | 20 |
| 58 | p-$ClC_6H_4$ | A | 238 | 39 |

a) See experimental section. b) Decomposition.

Table 3



| Compd. No | $R^3$ | Method[a] | Mp[b] (°C) | Yield (%) |
|---|---|---|---|---|
| 59 | Ph | A | 217 | 82 |
| 60 | p-$MeC_6H_4$ | A | 175 | 64 |
| 61 | p-$MeOC_6H_4$ | A | 191 | 48 |
| 62 | p-$ClC_6H_4$ | A | 231 | 50 |

a) See experimental section. b) Decomposition.

In the case of N-phenylurea, the primary nitrogen, which should be more nucleophilic, attacks at the β-carbon and subsequently cyclizes to give 1,4-diphenyl-6-methyl-2(1H)-pyrimidinone (54). On the contrary, comparing the nucleophilicities of two nitrogens of N-phenylthiourea, the secondary nitrogen is seemed to be more nucleophilic than the primary nitrogen due to a large contribution of isothiourea form. Thus, the secondary nitrogen selectively attacks at the β-carbon, and subsequently cyclizes to give 1,6-diphenyl-4-methyl-2(1H)-pyrimidinethione (59).

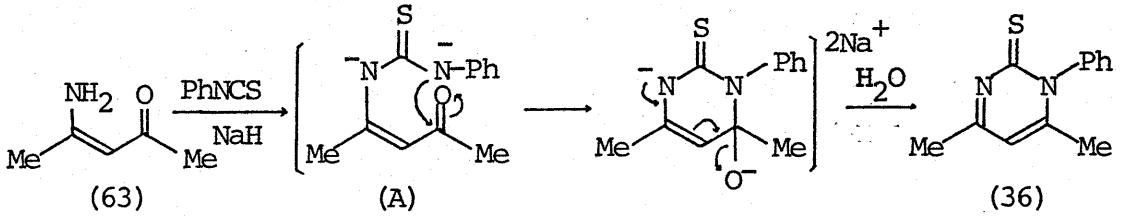
It is concluded that N-phenylurea reacts with benzoylacetone derivatives to give predominantly 1,4-diaryl-6-methyl-2(1H)-pyrimidinones, while N-phenylthiourea afforded only 1,6-diaryl-4-methyl-2(1H)-pyrimidinethiones. Therefore, the preparation of unsymmetrical 2(1H)-pyrimidinones becomes possible in this reaction.

## II-1-2 The Preparation from β-Aminoenones

The acylation of N-unsubstituted β-aminoenones easily occurs to give only N-acylated β-aminoenones at low temperature[116]. N-Unsubstituted β-aminoenones are treated with methyl iodide in the presence of excess sodium hydride on ice-bath to yield N,N-dialkylated β-aminoenones[117]. Further, amines undergo the addition reaction with isocyanates to give various ureas in quantitatively[118]. From these facts, it was expected that 2(1H)-pyrimidinones were obtained by the reaction of isocyanates with N-unsubstituted β-aminoenones and subsequent cyclization. Various β-aminoenones were prepared from the hydrogenation of 3,5-disubstituted isoxazoles[119].

Skötsch reported that 2-methyl-3-aminoacrolein was treated with phenyl isothiocyanate in acetonitrile under refluxing for 5 hr to afford 5-methyl-1-phenyl-2(1H)-pyrimidinethione in 51% yield[98]. When 2-amino-2-penten-4-one (63) reacted with phenyl isothiocyanate under the same condition, the expected 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) was obtained in only 5% yield. As the forcing condition, phenyl isothiocyanate in DMF was added dropwise to the solution of 63 in DMF in the presence of sodium hydride on ice-MeOH bath. After stirring for 2 hr, the reaction mixture was stirred for another 1 hr at room temperature to afford 36 in 53% yield. The reaction mechanism

is speculated as shown in Scheme 17. A nitrogen of β-amino-enone (63) attacks a thiocarbonyl carbon of phenyl isothio-cyanate to form the intermediate A. The intermediate A further cyclizes and then dehydrates to yield the product 36.



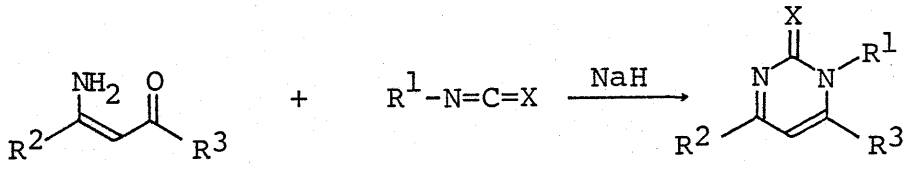

(63) (A) (36)

Scheme 17

Therefore, this reaction was applicable for the preparation of unsymmetrical 2(1H)-pyrimidinones. 2-Amino-2-hexen-4-one was treated with phenyl isothiocyanate to give 6-ethyl-4-methyl-1-phenyl-2(1H)-pyrimidinethione (68) in 58% yield. On the other hand, 4-amino-3-hexen-2-one afforded 4-ethyl-6-methyl-1-phenyl-2(1H)-pyrimidinethione (69, 50%) which was structurally isomeric with 68. The similar reaction of N-unsubstituted β-aminoenones with isocyanates was attempted, and the results were shown in Table 4.

In conclusion, the selective preparation of unsymmetrical 1-substituted 2(1H)-pyrimidinones is accomplished by the reaction of N-unsubstituted β-aminoenones with isocyanates in the presence of sodium hydride.

Table 4



| Compd. No | X | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|---|
| 64 | O | Ph | Me | Et | 20 |
| 65 | O | p-$ClC_6H_4$ | Me | Et | 29 |
| 66 | O | Ph | Me | $^nPr$ | 34 |
| 67 | O | p-$ClC_6H_4$ | Me | $^nPr$ | 36 |
| 68 | S | Ph | Me | Et | 58 |
| 69 | S | Ph | Et | Me | 50 |
| 54 | O | Ph | Ph | Me | 73[a)] |
| 70 | O | p-$ClC_6H_4$ | Ph | Me | 65 |
| 59 | S | Ph | Me | Ph | 68[a)] |
| 62 | S | Ph | Me | p-$ClC_6H_4$ | 65[a)] |
| 71 | S | Ph | Ph | Me | 64 |

a) Determined by PMR spectroscopy.

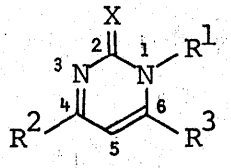
## II-2 The Structural Studies by Spectral Data

Few papers concerning the spectroscopic characteristics of 1-aryl-2(1H)-pyrimidinones have been reported. Since the spectra reflected the structure and property, the author studied the spectroscopic characteristics of some typical 1-aryl-2(1H)-pyrimidinones.

In the IR spectra, 1-aryl-2(1H)-pyrimidinones showed strong absorption bands in the region 1630-1670 $cm^{-1}$ due to the C=O stretching. On the other hand, 1-aryl-2(1H)-pyrimidinethiones displayed strong bands in the region 1260-1280 $cm^{-1}$ attributed to the C=S stretching. (Table 5) These C=X absorption bands are very similar to the typical C=X absorption bands of ureas. From these facts, 1-aryl-2(1H)-pyrimidinones should behave as the cyclic ureas.

The UV spectra of 1-aryl-2(1H)-pyrimidinones were measured in ethanol, and the data were listed in Table 5. The longest wavelength of 1-phenyl-2(1H)-pyrimidinone (23) appeared at 318 nm, while that of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) appeared at 304 nm. The similar behavior was also observed between 1-phenyl-2(1H)-pyrimidinethione (27) and 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36). From the blue-shift of the compound 32 and 36, it is supposed that the benzene ring twists out of the pyrimidine ring plane in order to prevent the repulsion between benzene ring and C-6 methyl group. Further, the pKa value of 1,4,6-trimethyl-

Table 5 IR and UV Spectra of 1-Aryl-2(1H)-pyrimidinones



| Compd. No | X | $R^1$ | $R^2$ | $R^3$ | νC=O ($cm^{-1}$) | νC=S ($cm^{-1}$) | $\lambda_{max.}^{EtOH}$ nm(logε) | | |
|---|---|---|---|---|---|---|---|---|---|
| 23 | O | Ph | H | H | 1670 | —— | —— | —— | 318(3.77) |
| 32 | O | Ph | Me | Me | 1660 | —— | 210(4.35) | —— | 304(3.98) |
| 40 | O | o-$MeC_6H_4$ | Me | Me | 1650 | —— | —— | —— | 306(3.83) |
| 54 | O | Ph | Ph | Me | 1630 | —— | 217(4.26) | 271(4.27) | 329(3.97) |
| 55 | O | Ph | Me | Ph | 1660 | —— | 235(4.18) | —— | 318(3.79) |
| 27 | S | Ph | H | H | —— | 1280 | 234(3.84) | 291(4.20) | 384(3.11) |
| 36 | S | Ph | Me | Me | —— | 1280 | 221(4.07) | 291(4.21) | 366(3.53) |
| 48 | S | o-$MeC_6H_4$ | Me | Me | —— | 1275 | 216(4.18) | 291(4.26) | 366(3.56) |
| 59 | S | Ph | Me | Ph | —— | 1260 | —— | 296(4.28) | 368(3.61) |
| 71 | S | Ph | Ph | Me | —— | 1280 | —— | 291(4.62) | 396(3.49) |

2(1H)-pyrimidinone (4) hydrochloride was reported to be 4.0 by Marshall[3]. The pKa value of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) hydrochloride was measured to be 3.3 by UV spectral method. Thus, 1-aryl-2(1H)-pyrimidinones are expected to form the salts in the presence of strong acids.

The CMR and PMR spectra were also measured, and the results were shown in Table 6 and 7. The signals of carbonyl carbons appeared at ca. 157 ppm. This chemical shift resembles the carbonyl carbon (164.4 ppm) of tetramethylurea. Breitmaier reported that 5-methyl-1-phenyl-2(1H)-pyrimidinethione exhibited the thiocarbonyl carbon at 182.9 ppm[98]. 1-Aryl-2(1H)-pyrimidinethiones showed the thiocarbonyl carbons at ca. 184 ppm. The chemical shift of C-5 carbon of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) was 105.3 ppm, while that of the corresponding 2(1H)-pyrimidinethione (36) was 112.2 ppm. (Table 6) In the PMR spectrum, the similar behavior was observed at olefinic protons of C-5 position. The chemical shift of an olefinic proton of the compound 32 was 6.20 ppm, while that of the compound 36 was 6.48 ppm. (Table 7) Stewart reported[120] that the rotational barrier around the carbon-nitrogen single bond for thioamides was 3-5 kcal $mol^{-1}$ higher than for the corresponding amides, and this difference can be attributed to more single bond character in the carbon-sulfur double bond in thioamides as a consequence of greater contribution of $-H\overset{+}{N}=C(S^{-})-$ character. Therefore, the lower shift of the

Table 6 CMR Spectra of 1-Aryl-2(1H)-pyrimidinones

| Compd. No | C-2 (s) | C-4 (s) | C-5 (d) | C-6 (s) | 4-Me (q) | 6-Me (q) | Aryl Ring |
|---|---|---|---|---|---|---|---|
| 32 | 156.9 | 156.8 | 105.3 | 175.8 | 25.3 | 21.0 | 127.3(d) 129.0(d) 129.8(d) 133.7(d) |
| 40 | 156.3 | 156.8 | 105.3 | 176.1 | 25.4 | 20.6 | 127.3(d) 127.6(d) 129.4(d) 131.6(d) 135.0(s) 136.8(s) |
| 54 | 157.3 | 157.9 | 101.7 | 170.9 | —— | 21.7 | 127.4(d) 127.9(d) 128.6(d) 129.1(d) 130.0(d) 131.8(d) 136.1(s) 137.9(s) |
| 55 | 158.8 | 157.2 | 106.8 | 176.6 | 25.4 | —— | 119.7(d) 122.4(d) 128.3(d) 128.6(d) 129.0(d) 129.8(d) 137.7(s) 139.6(s) |
| 36 | 184.6 | 157.6 | 111.2 | 169.6 | 25.0 | 22.3 | 126.8(d) 129.2(d) 130.2(d) 141.3(s) |
| 48 | 183.8 | 157.4 | 111.0 | 169.7 | 25.0 | 21.8 | 126.5(d) 128.0(d) 129.5(d) 131.9(d) 133.9(s) 140.2(s) |
| 59 | 184.9 | 159.2 | 111.4 | 169.7 | 25.2 | —— | 128.2(d) 128.3(d) 128.6(d) 129.2(d) 129.7(d) 133.2(s) 141.3(s) |
| 71 | 184.8 | 158.6 | 107.0 | 164.1 | —— | 22.9 | 126.8(d) 128.3(d) 128.7(d) 129.3(d) 130.3(d) 132.3(d) 135.0(s) 141.6(s) |

Table 7 PMR Spectra of 1-Aryl-2(1H)-pyrimidinones

| Compd. No | N-Me | 4-Me | 6-Me | 5-H | Aromatic |
|---|---|---|---|---|---|
| 4 | 3.59(s) | 2.33(s) | 2.38(d,J=0.7Hz) | 6.19(q,J=0.7Hz) | ——— |
| 32 | ——— | 2.40(s) | 1.98(d,J=0.7Hz) | 6.20(q,J=0.7Hz) | 7.1-7.6(m,5H) |
| 40 | 2.16(s)[a] | 2.48(s) | 1.95(d,J=0.7Hz) | 6.22(q,J=0.7Hz) | 7.1-7.3(m,4H) |
| 54 | ——— | ——— | 2.08(d,J=0.7Hz) | 6.72(q,J=0.7Hz) | 7.1-7.5(m,8H)<br>7.9-8.2(m,2H) |
| 55 | ——— | 2.40(s) | ——— | 6.20(s) | 7.0-7.2(m,10H) |
| 22 | 3.98(s) | 2.37(s) | 2.48(d,J=0.7Hz) | 6.48(q,J=0.7Hz) | ——— |
| 36 | ——— | 2.40(s) | 1.98(d,J=0.7Hz) | 6.52(q,J=0.7Hz) | 7.2-7.7(m,5H) |
| 48 | 2.10(s)[a] | 2.40(s) | 1.92(d,J=0.7Hz) | 6.56(q,J=0.7Hz) | 7.1-7.4(m,4H) |
| 59 | ——— | 2.49(s) | ——— | 6.60(s) | 7.1-7.4(m,10H) |
| 71 | ——— | ——— | 2.08(d,J=0.7Hz) | 7.09(q,J=0.7Hz) | 7.2-7.6(m,8H)<br>8.1-8.3(m,2H) |

a) The chemical shift of methyl protons of o-tolyl group.

compound 36 may be attributed to a larger deshielding effect from the pyrimidine ring, which is caused by the contribution of the polarized form. (Fig. 7)

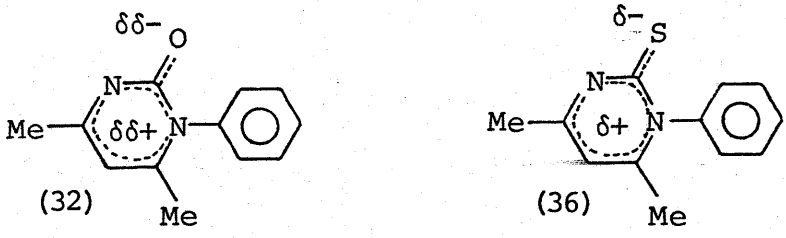



Fig. 7

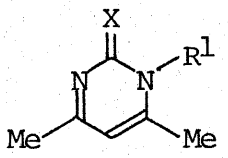
The assignment for the signals of C-4 and C-6 methyl protons was carried out as follows. C-6 methyl protons exhibited allyl coupling (J=0.7 Hz) with an olefinic proton in the pyrimidine ring, but C-4 methyl protons appeared as a singlet. 6-Methyl-1,4-diphenyl-2(1H)-pyrimidinone (54) and -thione (71) showed a benzoyl pattern. By the comparison of olefinic protons of 4,6-dimethyl-1-phenyl- (32) and 6-methyl-1,4-diphenyl-2(1H)-pyrimidinone (54), it was found that the olefinic proton of the compound 54 shifted 0.5 ppm to lower field by the deshielding effect of the conjugated phenyl ring at C-4 position. The similar deshielding effect was observed in the compound 71. This fact shows that the phenyl group at C-4 position should be co-planar with the pyrimidine ring. When the chemical shift of C-6 methyl protons of 1,4,6-trimethyl-2(1H)-pyrimidinone (4) compared with that of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32), the higher-field shift of C-6 methyl protons of the compound 32 was observed.

The similar shift was observed in various 1-aryl-2(1H)-pyrimidinones. (Table 8) The differences of the chemical shift ($\Delta\delta$) were also listed in Table 8.

$$\Delta\delta = - ( \delta^{6\text{-Me}}_{1\text{-Aryl}} - \delta^{6\text{-Me}}_{1\text{-Me}} )$$

Where $\delta^{6\text{-Me}}_{1\text{-Aryl}}$ was the chemical shift of C-6 methyl protons of 1-aryl-2(1H)-pyrimidinones, and $\delta^{6\text{-Me}}_{1\text{-Me}}$ was that of 1,4,6-trimethyl-2(1H)-pyrimidinone (4) or the corresponding 2(1H)-pyrimidinethione (22). This higher-field shift should be caused by the shielding effect of the aryl ring at N-1 position. In addition to the fact supposed from the blue-shift of the compounds 32 and 36, this fact suggests that the pyrimidine ring is nearly perpendicular to the aryl ring in the most stable conformation. An aniline derivative generally has the co-planar conformation between benzene ring and amino plane by the resonance of nitrogen and benzene. Therefore, it seems that the steric hindrance of the pyrimidine and aryl ring exists in 1-aryl-4,6-dimethyl-2(1H)-pyrimidinones, and free rotation around the carbon-nitrogen single bond is restricted.

Table 8 The Differences of the Chemical Shift ($\Delta\delta$) of C-6 Methyl Protons




| Compd. No | X | $R^1$ | $\delta$(6-Me) (ppm) | $\Delta\delta^{a)}$ (ppm) | Compd. No | X | $R^1$ | $\delta$(6-Me) (ppm) | $\Delta\delta^{a)}$ (ppm) |
|---|---|---|---|---|---|---|---|---|---|
| 4 | O | Me | 2.38 | ——— | 45 | O | o-$ClC_6H_4$ | 2.03 | +0.35 |
| 32 | O | Ph | 1.98 | +0.40 | 46 | O | o-$BrC_6H_4$ | 1.95 | +0.43 |
| 38 | O | m-$MeC_6H_4$ | 1.98 | +0.40 | 22 | S | Me | 2.48 | ——— |
| 39 | O | m-$MeOC_6H_4$ | 1.95 | +0.43 | 36 | S | Ph | 1.98 | +0.50 |
| 40 | O | o-$MeC_6H_4$ | 1.95 | +0.43 | 48 | S | o-$MeC_6H_4$ | 1.92 | +0.56 |
| 41 | O | o-$MeOC_6H_4$ | 1.98 | +0.40 | 49 | S | o-$MeOC_6H_4$ | 2.00 | +0.48 |
| 42 | O | o-$EtC_6H_4$ | 1.89 | +0.49 | 50 | S | o-$EtC_6H_4$ | 1.94 | +0.54 |
| 43 | O | o-$EtOC_6H_4$ | 1.97 | +0.41 | 51 | S | o-$EtOC_6H_4$ | 2.00 | +0.50 |
| 44 | O | o-$FC_6H_4$ | 1.98 | +0.40 | 52 | S | o-$ClC_6H_4$ | 1.98 | +0.50 |

a) $\Delta\delta = -\left( \delta^{6\text{-Me}}_{1\text{-Aryl}} - \delta^{6\text{-Me}}_{1\text{-Me}} \right)$

## II-3 The Restricted Rotation Around the Carbon-Nitrogen Single Bond[121),122)]

In the previous section (II-2), the pyrimidine ring was found to be nearly perpendicular to the aryl ring in the most stable conformation by the steric interaction between the aryl ring and C-6 methyl group in the pyrimidine ring. Although 1-aryl-2(1H)-pyrimidinones consisted of large number of atoms more than 30, the author attempted the calculation of the most stable conformation and rotational barrier around the carbon-nitrogen single bond. Since Force-field method[123),124)] is superior in the calculation of the conformation and potential energy of large molecules, it seemes to be the most suitable method for this calculation. Further, Yamamoto modified ordinary Force-field method for applying to heterocyclic compounds[117)]. Therefore, the rotational barrier around the carbon-nitrogen single bond of 1-aryl-2(1H)-pyrimidinones was calculated by the Force-field method. In the case of 4,6-dimethyl-1-(o-tolyl)-2(1H)-pyrimidinone (40), the relation between dihedral angle ($\theta$) around the carbon-nitrogen single bond and potential energy (E) was shown in Fig. 8. From this calculation, the dihedral angle of the most stable conformation was found to be 41°, and the rotational barrier was 39.5 kcal $mol^{-1}$. Furthermore, this result indicated that the repulsion between the C-6 methyl group and the aryl-methyl group was much greater than

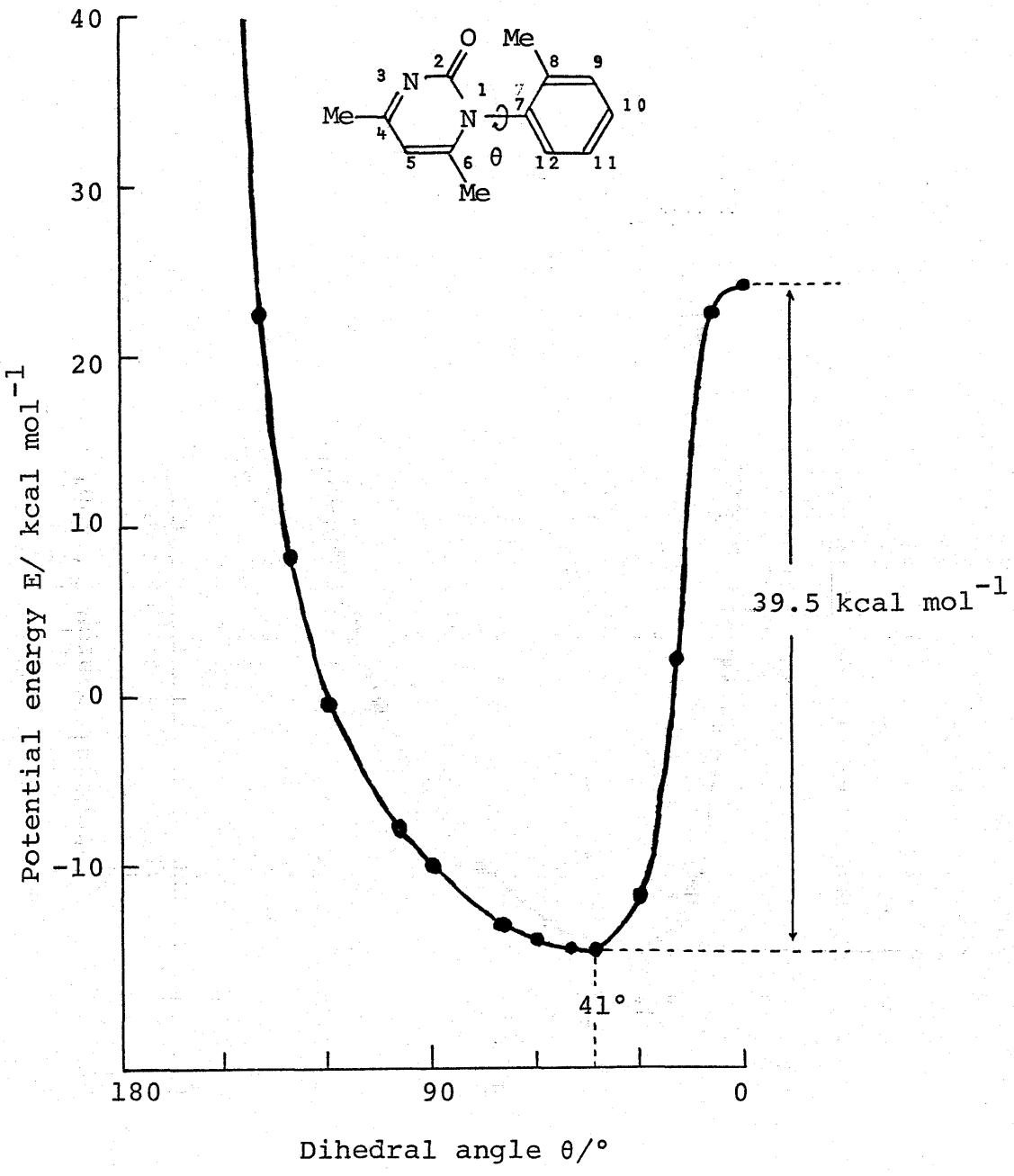


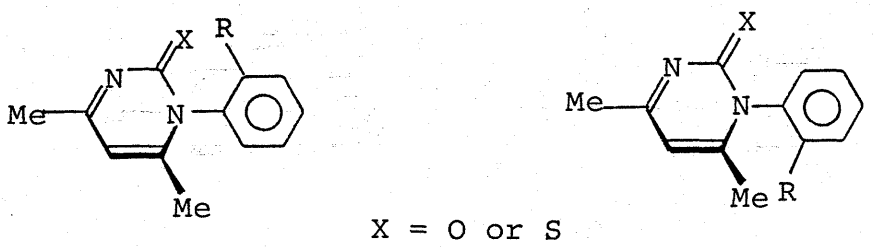

Fig. 8 Potential Energy of 4,6-Dimethyl-1-(o-tolyl)-2(1H)-pyrimidinone (40) as a Function of the Dihedral Angle θ.

Table 9 Rotational Barriers Calculated by Force-field Method

| Compd. No | $r$[a] (Å) | $\theta$[b] (°) | $E_{t.s.}$[c] (kcal mol$^{-1}$) | $r$[a] (Å) | $\theta$[b] (°) | $E_{m.s.}$[d] (kcal mol$^{-1}$) | $\Delta H^{\neq}$[e] (kcal mol$^{-1}$) |
|---|---|---|---|---|---|---|---|
| 23 | 1.45 | 90 | 2.4 | 1.48 | 0 | -4.3 | 6.7 |
| 38 | 1.51 | 0 | 9.6 | 1.46 | 49 | -5.1 | 14.7 |
| 39 | 1.51 | 0 | 10.1 | 1.46 | 59 | -2.9 | 13.0 |
| 40 | 1.54 | 5.6 | 34.3 | 1.46 | 41 | -5.2 | 39.5 |
| 41 | 1.53 | 4.3 | 31.4 | 1.49 | 53 | 1.2 | 30.2 |
| 42 | 1.56 | 7.3 | 37.6 | 1.47 | 42 | -4.9 | 42.5 |

a) $C_7$-$N_1$ Single bond length. b) Dihedral angle between $C_2$-$N_1$ and $C_7$-$C_8$ bond. c) Potential energy in transition state. d) Potential energy in the most stable conformation. e) $\Delta H^{\neq} = E_{t.s.} - E_{m.s.}$

that between the aryl-methyl group and the carbonyl oxygen. In the same way, the rotational barriers for 1-(o-substituted)phenyl-4,6-dimethyl-2(1H)-pyrimidinones (41 and 42) were calculated to be 30.2 and 42.5 kcal $mol^{-1}$, respectively. On the other hand, the rotational barriers for 1-(m-substituted)phenyl-4,6-dimethyl-2(1H)-pyrimidinones (38 and 39) were calculated to be 14.7 and 13.0 kcal $mol^{-1}$, respectively. Further, 1-phenyl-2(1H)-pyrimidinone (23) was found to be co-planar in the most stable conformation. (Table 9) Since the minimum rotational barrier is ca. 23 kcal $mol^{-1}$ in order to separate isomers at room temperature[125], the author predicts that the two rotational isomers of 1-(o-substituted)phenyl-4,6-dimethyl-2(1H)-pyrimidinones should be separable. (Fig. 9)

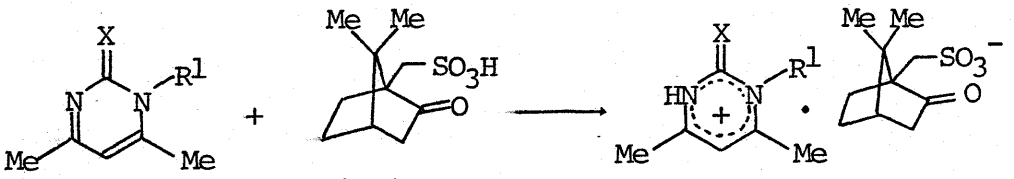



X = O or S

Fig. 9

For proving the result of the calculation, the author tried to resolve the optically active 1-aryl-2(1H)-pyrimidinones by the fractional recrystallization. Since the pKa value of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) hydrochloride was measured to be 3.3 by UV spectral method, D-camphor-10-sulfonic acid (72) was used as the resolving agent.

Table 10 The Pyrimidinium Salts



(72)

| Compd. No | X | $R^1$ | Mp (decomp. °C) | Yield (%) |
|---|---|---|---|---|
| 73 | O | m-$MeC_6H_4$ | 206 | 98 |
| 74 | O | m-$MeOC_6H_4$ | 179 | 97 |
| 75 | O | o-$MeC_6H_4$ | 217 | 90 |
| 76 | O | o-$MeOC_6H_4$ | 200 | 95 |
| 77 | O | o-$EtC_6H_4$ | 182 | 98 |
| 78 | O | o-$ClC_6H_4$ | 213 | 97 |
| 79 | S | o-$MeC_6H_4$ | 227 | 90 |
| 80 | S | o-$MeOC_6H_4$ | 202 | 88 |
| 81 | S | o-$EtC_6H_4$ | 206 | 96 |
| 82 | S | o-$EtOC_6H_4$ | 198 | 90 |
| 83 | S | o-$ClC_6H_4$ | 225 | 94 |
| 84 | S | o-Me-m-$ClC_6H_3$ | 218 | 89 |

The optically active 1-aryl-2(1H)-pyrimidinones were obtained by recrystallization of the salts (73-84), which were formed from racemic 1-aryl-2(1H)-pyrimidinones with D-camphor-10-sulfonic acid, followed by neutralization. (Table 10) The specific rotation of 1-aryl-2(1H)-pyrimidinones was listed in Table 11.

Table 11

| Compd. No | Concentration[a] | $[\alpha]_D^{25}$ (°) | Compd. No | Concentration[a] | $[\alpha]_D^{25}$ (°) |
|---|---|---|---|---|---|
| 38 | 0.6 | 0 | 48 | 1.0 | -23.4 (-200)[b] |
| 39 | 0.8 | 0 | 49 | 2.2 | +0.6 |
| 40 | 0.6 | -6.2 (-120)[b] | 50 | 1.1 | -0.4 |
| 41 | 0.8 | +0.4 | 52 | 1.9 | +3.3 |
| 42 | 0.5 | +4.5 | 53 | 1.0 | +6.5 |
| 45 | 0.8 | -1.4 | | | |

a) Grams per 100 ml. b) Absolute rotation.

1-(m-Substituted)phenyl-4,6-dimethyl-2(1H)-pyrimidinones (38 and 39) exhibited no specific rotation. On the contrary, 1-(o-substituted)phenyl-4,6-dimethyl-2(1H)-pyrimidinones showed specific rotations. In the case of 4,6-dimethyl-1-(o-tolyl)-2(1H)-pyrimidinone (40) and the corresponding 2(1H)-

pyrimidinethione (48), the absolute rotation was determined by means of the PMR spectrum in the presence of the chiral reagent, tris[3-(trifluoromethylhydroxymethylene)-D-camphorato]europium(III) [Eu(tfc)$_3$]. The fact that 1-(o-substituted)phenyl-4,6-dimethyl-2(1H)-pyrimidinones not m-substituted derivatives are separated in optically active forms, is good agreement with the calculation based upon the Force-field method.

To clarify the relation between rotational barrier and the calculated values, the rate of racemization of optically active 1-aryl-2(1H)-pyrimidinones was studied. Arrhenius plots showed a good linear relation, and the activation parameters were obtained as shown in Table 12. The activation energy (Ea) was found to be in the range from 30.1 to 34.0 kcal mol$^{-1}$, and the free energy of activation ($\Delta G^{\neq}$) and activation enthalpy ($\Delta H^{\neq}$) were found to be larger than 26.6 and 29.4 kcal mol$^{-1}$, respectively. In the case of 48 and 53, the buttressing effect[126)-128)] by chlorine, which was introduced into metha-position of the aryl ring, was not observed. These activation parameters are good agreement with the expectation from the Force-field calculation.

The standard bond length of C=O double bond is 1.22 Å, and that of C=S double bond is 1.71 Å. The van der Waals radius of oxygen is 1.4 Å, and that of sulfur is 1.85 Å. From these facts, the rotational barrier was expected to increase when a sulfur replaced oxygen. However, the

Table 12 Activation Parameters of 1-Aryl-4,6-dimethyl-2(1H)-pyrimidinones

| Compd. No | Ea (kcal $mol^{-1}$) | $\Delta G^{\neq}$ (kcal $mol^{-1}$) | $\Delta H^{\neq}$ (kcal $mol^{-1}$) | $\Delta S^{\neq}$ (cal $K^{-1}$ $mol^{-1}$) |
|---|---|---|---|---|
| 40 | 31.8 | 30.3 | 31.2 (39.5)[a] | 2.9 |
| 42 | 34.0 | 30.2 | 33.3 (42.5)[a] | 8.0 |
| 48 | 31.5 | 27.7 | 30.8 | 8.8 |
| 52 | 30.1 | 26.6 | 29.4 | 7.9 |
| 53 | 31.1 | 27.0 | 30.4 | 9.5 |

a) Calculated value by means of Force-field method.

rotation barrier of 4,6-dimethyl-1-(o-tolyl)-2(1H)-pyrimidinone (40) was nearly equal that of the corresponding 2(1H)-pyrimidinethione (48). (Table 12) Comparing the CMR and PMR spectra of 40 and 48, the lower-field shifts of C-5 carbon and C-5 olefinic proton of 48 were observed by a larger deshielding effect from the pyrimidine ring, which was caused by the contribution of the polarized form as shown in Fig. 7. Furthermore, the greater single bond character would cause a decrease in the interatomic repulsion between the sulfur atom and the ortho-methyl group on the pyrimidine ring. The fact that rotational barrier of 40 was nearly equal that of 48, was explained by the larger van der Waals radius of sulfur atom, and the longer single bond length and the larger single bond character of C=S double bond.

The resolution of optically active 1-aryl-2(1H)-pyrimidinones is the first example, to the best of a knowledge. Further, the author believes that these results give very important information for studying the rotational barrier around the carbon-nitrogen single bond between nucleic acid bases and riboses in nucleosides.

## II-4 The Antiinflammatory Activity[129)]

Recently there have been some reports[66),91),130)] on the pharmaceutical activity of 1-unsubstituted or 1-alkyl-2(1H)-pyrimidinones. Whereas the pharmaceutical activity of 1-aryl-2(1H)-pyrimidinones has not been reported. As a part of the investigation about the properties, the author tested the antiinflammatory activity of 1-aryl-2(1H)-pyrimidinones and their D-camphor-10-sulfonates.

The inhibition (%) was listed in Table 13. The control experiment was carried out by using acetyl salicylic acid (aspirin). Four kinds of 2(1H)-pyrimidinones (32, 40, 43 and 44) and two 2(1H)-pyrimidinethiones (48 and 49) exhibited potent antiinflammatory activity more than 40%. As the side-effect, the convalsion occurred in the case of three samples (45, 46, and 52) which were introduced halogen atoms on the aryl ring at N-1 position. The $LD_{50}$ value was measured in the case of above six samples by giving os to mice at a dosage of 500 mg $kg^{-1}$. As a general standard, the hopeful drug was excluded death samples at a dosage of 500 mg $kg^{-1}$. However, the $LD_{50}$ value of these samples was found to be less than 500 mg $kg^{-1}$.

It is concluded that four kinds of 2(1H)-pyrimidinones and two 2(1H)-pyrimidinethiones exhibit potent antiinflammatory activity, but the safety area of these compounds is narrow from the result of the $LD_{50}$ value.

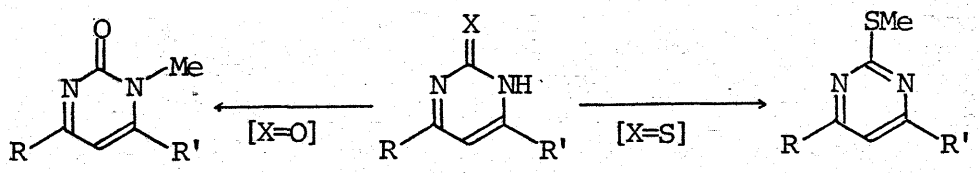
Table 13 The Antiinflammatory Activity

| Sample No | Inhibition (%) 3 hr | 4 hr | Sample No | Inhibition (%) 3 hr | 4 hr |
|---|---|---|---|---|---|
| 32 | 43.4 | 29.1 | 49 | 69.3 | 45.7 |
| 36 | 9.9 | 20.3 | 50 | 18.2 | 10.8 |
| 38 | 7.3 | 3.8 | 51 | 0.9 | 3.1 |
| 39 | 24.6 | 16.2 | 52 | (death) | |
| 40 | 59.9 | 47.4 | 53 | 11.6 | 11.4 |
| 41 | 14.2 | 5.6 | 59 | 14.8 | -1.4 |
| 42 | 34.8 | 25.1 | 79 | 27.5 | 6.0 |
| 43 | 86.1 | 84.0 | 80 | -25.3 | —— |
| | (diarrhoea) | | 82 | 6.6 | —— |
| 44 | 74.6 | 73.0 | 83 | (death) | |
| 45 | (convalsion) | | 84 | 11.1 | —— |
| 46 | (convalsion) | | Aspirin[a)] | 25.9 | 20.7 |
| 48 | 43.3 | 38.0 | | | |

a) The control experiment was carried out by using of aspirin.

## III CHEMICAL REACTIONS OF 1-ARYL-2(1H)-PYRIMIDINONES

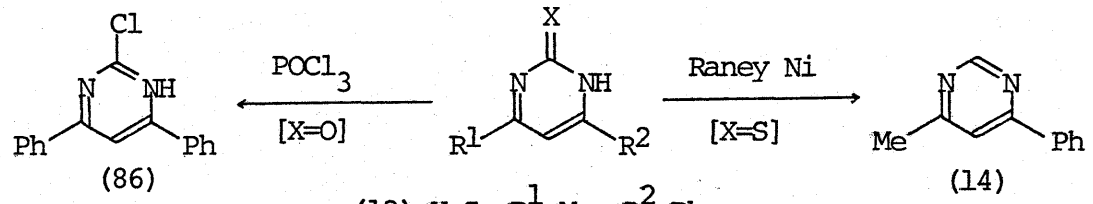
2(1H)-Pyrimidinones have many reaction sites for both electrophiles and nucleophiles. Many papers concerning the reaction of 1-unsubstituted 2(1H)-pyrimidinones have been reported. In the case of 1-unsubstituted 2(1H)-pyrimidinones, methylation occurs on nitrogen atoms to give N-methylated products[66),131)]. On the contrary, in the case of 2(1H)-pyrimidinethiones, methylation occurs on sulfur atoms to give S-methylated products[46)-48)]. (Scheme 18)




Scheme 18

From the fact that 4,6-diphenyl-2(1H)-pyrimidinone (85) is treated with phosphorus oxychloride to yield 2-chloro-4,6-diphenylpyrimidine (86)[75)] and 2(1H)-pyrimidinethiones are inert to this reagent, chlorination is characteristic reaction for 2(1H)-pyrimidinones. On the other hand, desulfuration is characteristic reaction for 2(1H)-pyrimidinethiones. For example, 4-methyl-6-phenyl-2(1H)-pyrimidinethione (13) is treated with Raney nickel to give 4-methyl-6-phenylpyrimidine (14)[71)]. (Scheme 19) Since methyl protons adjacent to heterocycles are activated by electron-

withdrawing effect of heteroaromatic ring, the reaction with nucleophiles can be expected on methyl group of 2(1H)-pyrimidinones.




(86)

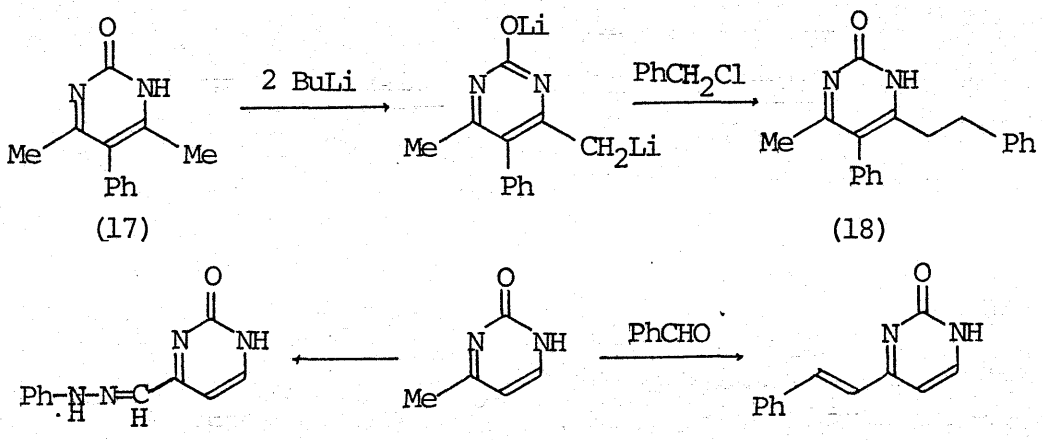
(13) X=S, $R^1$=Me, $R^2$=Ph

(85) X=O, $R^1$=$R^2$=Ph

(14)

Scheme 19

Treatment of 4,6-dimethyl-5-phenyl-2(1H)-pyrimidinone (17) with n-butyl lithium and subsequent trapping with benzyl-chloride afford 4-methyl-5-phenyl-6-phenetyl-2(1H)-pyrimidinone (18)[79),80)]. The Aldol type condensation[81),82)] and diazo-coupling[85)] of methyl group have been also reported. (Scheme 20)

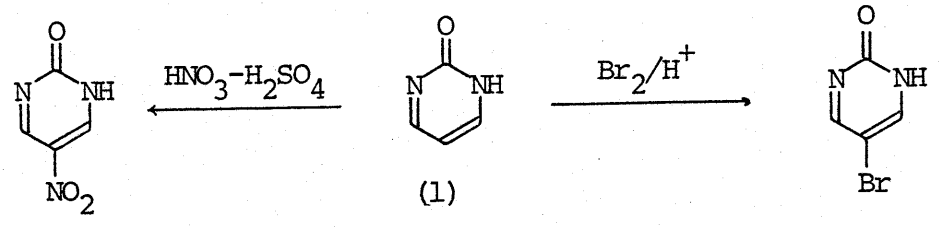



(17)

(18)

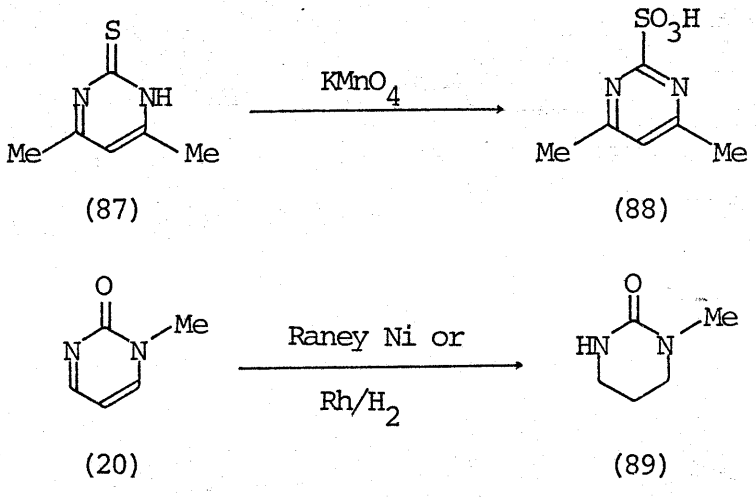
Scheme 20

The nitration[86] and bromination[87)-89)] at C-5 position of 2(1H)-pyrimidinone (1) have been studied by Fox and Tee, respectively. (Scheme 21)



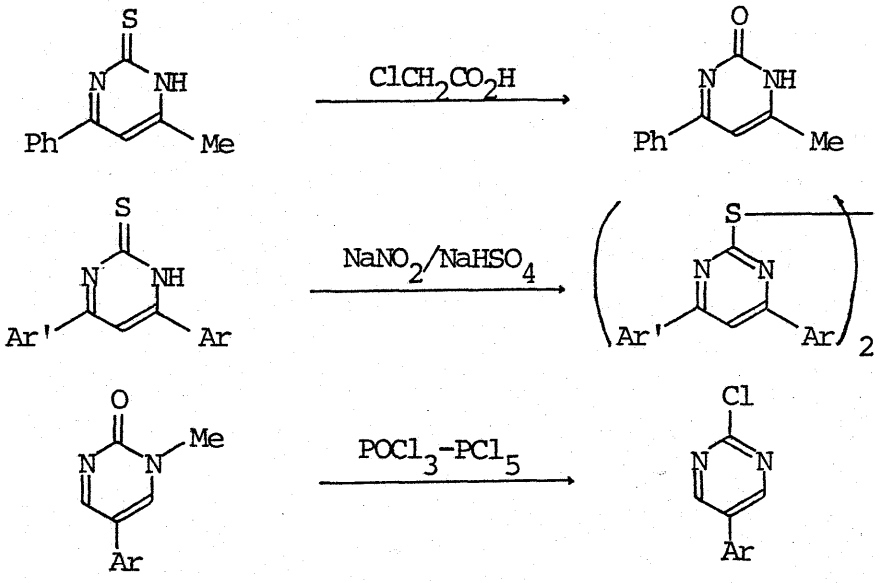

Scheme 21

4,6-Dimethyl-2(1H)-pyrimidinethione (87) is oxidized with potassium permanganate to give 4,6-dimethyl-2-sulfonylpyrimidine (88)[132]. 1-Methyl-2(1H)-pyrimidinone (20) is hydrogenated on Raney nickel or rhodium to yield tetrahydro-1-methyl-2(1H)-pyrimidinone (89)[26]. (Scheme 22)




Scheme 22

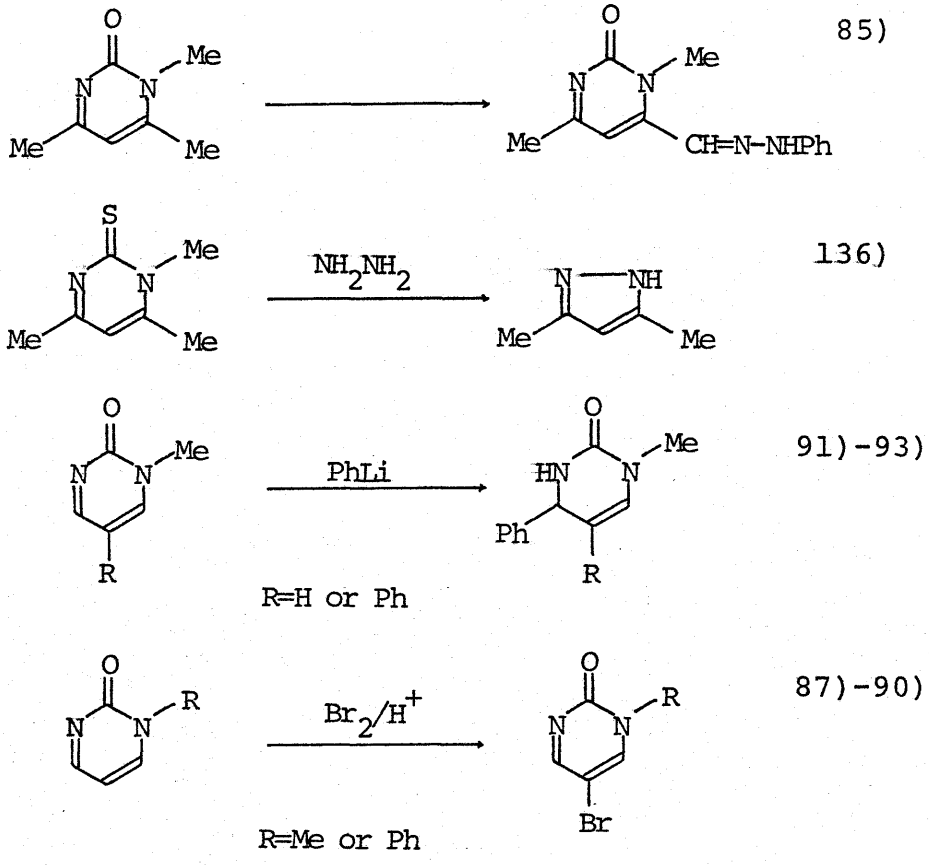
The exchange reaction of thiocarbonyl to carbonyl group[133] and the dimerization[46),47)] of 2(1H)-pyrimidinethiones, and the abnormal demethylation of 1-methyl-5-aryl-2(1H)-pyrimidinones[134),135)] have been also reported. (Scheme 23)




Scheme 23

As mentioned above, the reaction of 1-unsubstituted 2(1H)-pyrimidinones with electrophiles has been extensively investigated. On the contrary, the electrophilic and nucleophilic reactions of 1-substituted 2(1H)-pyrimidinones have not been reported except four types of reactions as shown in Scheme 24. In addition, 1-substituent group is quite necessary to study the regioselective reaction of 2(1H)-pyrimidinones because of the inhibition of the tautomerism. Therefore, the author investigated the electro-

philic and nucleophilic reactions of 1-aryl-2(1H)-pyrimidinones.




Scheme 24

Although the photochemical reaction is considered to be a part of chemical reactions, little attention has been paid to the photochemical reaction of 2(1H)-pyrimidinones. The only one photochemical reaction of 2(1H)-pyrimidinones have been reported by Pfoertner[97]. Thus, the author also investigated the photochemical reaction of 1-aryl-2(1H)-pyrimidinones.

## III-1 The Chemical Properties

Generally, electron density is the good index for studying the chemical behaviors of organic molecules. The INDO calculation was carried out for the purpose of the prediction of reaction sites of 2(1H)-pyrimidinones. Here the coordinates of each atom in the most stable conformation of 2(1H)-pyrimidinones, which were derived from Force-field method, were used for this INDO calculation. By Force-field calculation, 1-phenyl-2(1H)-pyrimidinone (23) was proposed to be co-planar between the pyrimidine and phenyl ring.

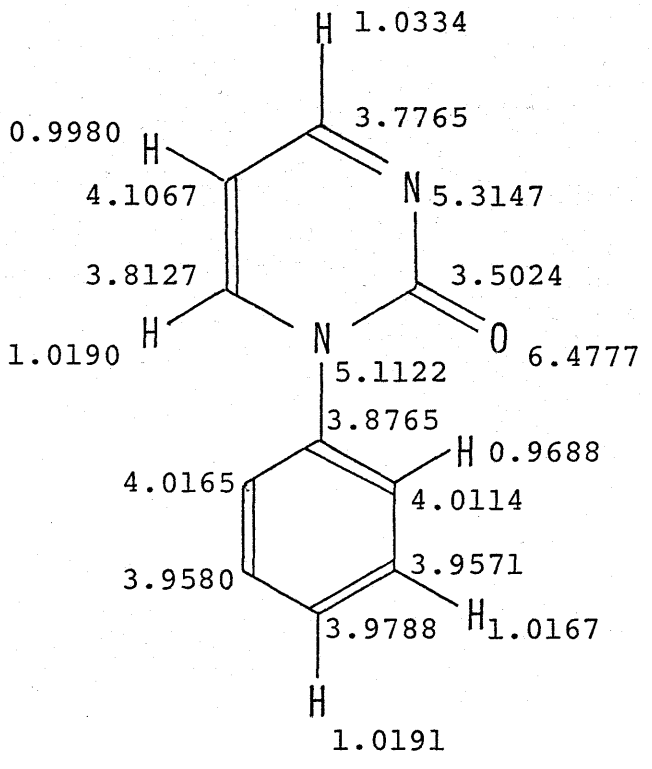



Fig. 10

The INDO calculation of the compound 23 was carried out, and the resulting atomic population was shown in Fig. 10. On the contrary, 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) was found to be twisted about 41° by the steric interaction between C-6 methyl and phenyl ring. The resulting atomic population of the compound 32 was also shown in Fig. 11.

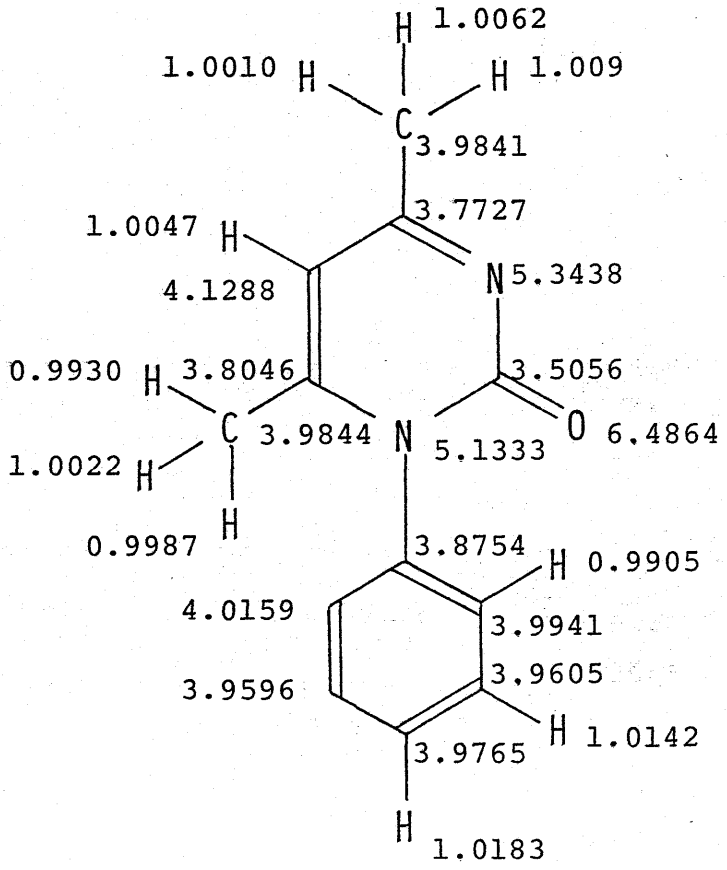
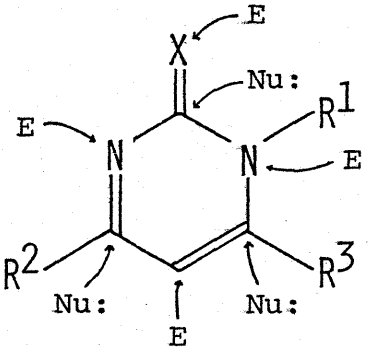



Fig. 11

These results indicate that 2(1H)-pyrimidinones have many reaction sites for electrophiles and nucleophiles. The carbonyl oxygen, N-1 and N-3 nitrogen, and C-5 olefinic carbon

are expected to be attacked by electrophiles. On the contrary, C-2, C-4 and C-6 carbon are expected to be attacked by nucleophiles. (Fig. 12)



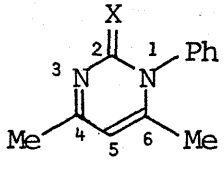

X = O or S

Fig. 12

In the case of 2(1H)-pyrimidinethiones, the author could not calculate the atomic population unfortunately owing to the lack of the INDO parameters concerning sulfur atom. Therefore, the reaction indexes about 2(1H)-pyrimidinethiones were calculated by means of HMO method. The superdelocalizability for electrophiles ($S_r^E$) was calculated by HMO method, and the results were shown in Table 14.

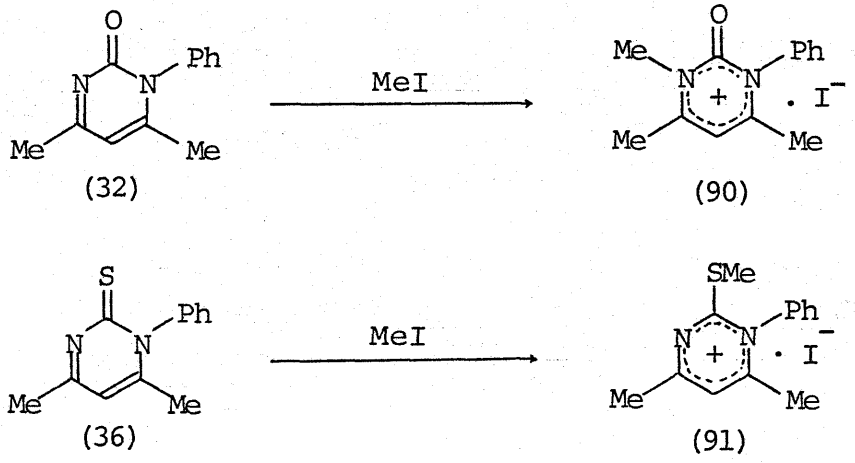
Table 14

The Superdelocalizability for Electrophiles ($S_r^E$)




| Compd. No | X | X | N-1 | N-3 |
|---|---|---|---|---|
| 32 | O | 0.9323 | 0.9461 | 1.0827 |
| 36 | S | 1.6424 | 1.0774 | 1.3395 |

The greatest $S_r^E$ value of 2(1H)-pyrimidinone (32) is on N-3 nitrogen, while that of 2(1H)-pyrimidinethione (36) is on thiocarbonyl sulfur. Actually, 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) reacted with methyl iodide to give the N-methylated product, 1,2-dihydro-3,4,6-trimethyl-2-oxo-1-phenylpyrimidinium iodide (90) in quantitatively. On the other hand, 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) afforded the S-methylated product, 4,6-dimethyl-2-methylthio-1-phenylpyrimidinium iodide (91) in quantitatively. (Scheme 25)




Scheme 25

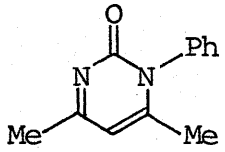
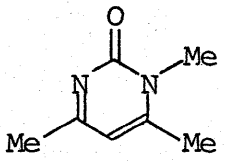
## III-2 The Reaction with Electrophiles

### III-2-1 H-D Exchange Reaction

It is well known that methyl groups are activated by the adjacent aromatic ring, especially nitrogen containing heteroaromatic ring. For example, a methyl group of 2-methylpyridine[77] or 4,6-dimethylpyrimidine 1-oxide[137] is easily deprotonated by a base to give carbanion, which reacts with various electrophiles to give the substitution products on a methyl group. The reactivity of such activated methyl groups was observed in the deuterium exchange reaction by the treatment with deuterium oxide or deutero-methanol in the presence of base. Batterham[138] and Stewart[139] reported that methyl protons at C-6 position of 1,4,6-trimethyl-2(1H)-pyrimidinone (4) were deuterated faster than those of C-4 position in deuterium oxide in the presence of sodium deuteroxide. Similarly the author attempted the deuterium exchange of methyl protons of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32). In the presence of sodium methoxide in $d_1$-methanol, the compound 32 was stirred for 1 hr to yield completely deuterated 2(1H)-pyrimidinone both at C-4 and C-6 methyl protons. When potassium carbonate was used as base, C-4 and C-6 methyl protons were deuterated about 17 and 34%, respectively. From these results listed in Table 15, it was found that C-4 methyl protons were

Table 15

Deuterium Exchange of 4,6-Dimethyl-1-phenyl-2(1H)-pyrimidinone

| | Conditions | Time (min) | D-Exchange (%) (C-4 Me) | (C-6 Me) |
|---|---|---|---|---|
|  | MeOD/MeONa | 60 | 100 | 100 |
| | MeOD/MeONa | 30 | 100 | 100 |
| | $D_2O$-MeOH/$K_2CO_3$ | 30 | 23 | 76 |
| | $D_2O/K_2CO_3$ | 40 | 17 | 34 |
|  | $D_2O$/NaOD | 1 | 12 | 50[a)] |

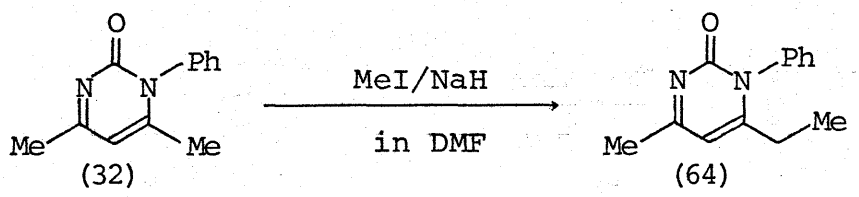
a) See Lit. 138.

deuterated more easily than C-4 methyl protons. However, the regioselectivity of the compound 32 seemed to be inferior to that of 1,4,6-trimethyl-2(1H)-pyrimidinone owing to the twisted conformation.

## III-2-2 The Regioselective C-Alkylation

The C-alkylation of methyl group of 1-unsubstituted 2(1H)-pyrimidinones such as 4,6-dimethyl-5-phenyl-2(1H)-pyrimidinone[79),80)] has been reported by Murray. Whereas the C-alkylation of 1-substituted 2(1H)-pyrimidinones has not been reported. From the result of deuterium exchange, the regioselective C-alkylation was expected at C-6 methyl group by the reaction of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) with alkyl halides in the presence of base. By using LPC, the optimum condition was found to be used sodium hydride as a base in DMF. (Table 16)

Table 16



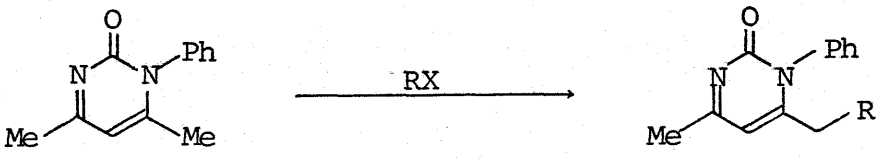

(32) (64)

| Ratio 32 : NaH : MeI | Time (hr) | Yield (64,%) | Yield (32,%) |
|---|---|---|---|
| 1 : 1.5 : 6 | 2 | 15 | 4 |
| 1 : 1.5 : 6 | 1 | 34 | 9 |
| 1 : 1.5 : 6 | 0.5 | 31 | 40 |
| 1 : 1.2 : 6 | 1 | 22 | 18 |
| 1 : 1.5 : 1.2 | 1 | 14 | 38 |

* All experiments were carried out in ice-MeOH.

Under the optimum condition, the compound 32 was treated with methyl iodide in the presence of sodium hydride in DMF to give 6-ethyl-4-methyl-1-phenyl-2(1H)-pyrimidinone (64) in 34% yield, which was methylated regioselectively at C-6 methyl group. The similar C-alkylation with alkyl halides was attempted, and the results were summarized in Table 17.

Table 17 The Regioselective C-Alkylation

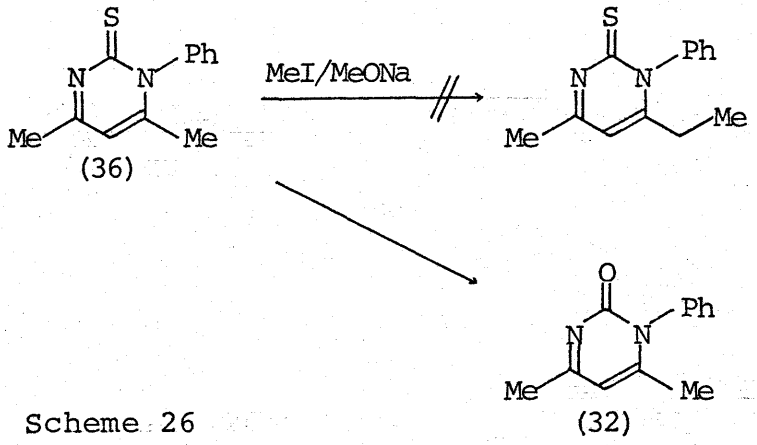



| Product | R | X | Yield(%) |
|---|---|---|---|
| 64 | Me | I | 34 |
| 66 | Et | I | 35 |
| 66 | Et | Br | 13 |
| 92 | $CH_2$=CH-$CH_2$ | I | 25 |
| 93 | $PhCH_2$ | Br | 30 |

In conclusion, the regioselective C-alkylation at C-6 methyl group of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone becomes possible by the treatment with alkyl halides in the presence of sodium hydride for preparing unsymmetrical 2(1H)-pyrimidinones.

## III-2-3 The Conversion of Thiocarbonyl into Carbonyl Group[113)]

Although 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) was also alkylated by using sodium methoxide, the yield was very poor. In the case of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) with methyl iodide, the expected C-methylation did not occur, but the corresponding 2(1H)-pyrimidinone (32) was obtained in 80% yield. (Scheme 26)

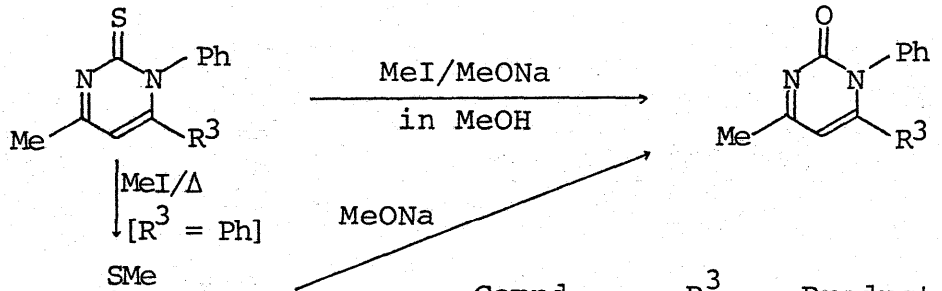



Scheme 26

Kröger reported that the hydrolysis of 2-methylthio-4-amino-1-methylpyrimidinium iodide gave the corresponding 2(1H)-pyrimidinone in the presence of base[140)]. Thus, 2-methylthio-1,6-diphenyl-4-methylpyrimidinium iodide (94), which was derived from 59 by heating with methyl iodide, afforded 55 in 80% yield by the treatment with sodium methoxide in methanol. Therefore, the conversion of thiocarbonyl into carbonyl group perhaps proceeds via methylpyrimidinium salt. Further, this conversion was applied for

preparing unsymmetrical 2(1H)-pyrimidinones. By treatment with methyl iodide in the presence of sodium methoxide, 2(1H)-pyrimidinethione (59) was successfully converted in 85% yield into the corresponding 2(1H)-pyrimidinone (55) which was the minor product from benzoylacetone and N-phenylurea. Other 2(1H)-pyrimidinethiones (60 and 62) were also converted in a similar fashion into the corresponding 2(1H)-pyrimidinones (95 and 96) in 79 and 54% yield, respectively. (Table 18)

Table 18




(94)

| Compd. No | $R^3$ | Product No. | Yield (%) |
|---|---|---|---|
| 59 | Ph | 55 | 85 |
| 60 | p-$MeC_6H_4$ | 95 | 79 |
| 62 | p-$ClC_6H_4$ | 96 | 54 |

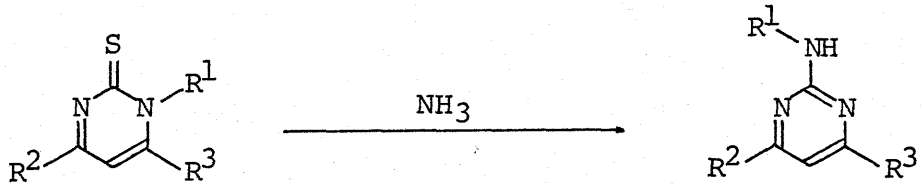
In conclusion, the conversion of thiocarbonyl into carbonyl group becomes possible by the treatment with methyl iodide in the presence of sodium methoxide. Also this conversion is applied for preparing unsymmetrical 2(1H)-pyrimidinones.

## III-3 The Reaction with Nucleophiles

### III-3-1 The Reaction with Amines[141)]

From the result of INDO calculation, it was predicted that C-2, C-4 and C-6 carbon was easily attacked by nucleophiles. First the author investigated the reaction of 1-aryl-2(1H)-pyrimidinones with ammonia as a nucleophile. 4,6-Dimethyl-1-phenyl-2(1H)-pyrimidinone (32) was heated with ammonia in a sealed tube, but the starting material 32 was recovered. On the contrary, 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) was also heated with ammonia to give 2-anilino-4,6-dimethylpyrimidine (97) in 36% yield. This compound 97 was found to be identical with an authentic sample prepared from 2-chloro-4,6-dimethylpyrimidine and aniline[70),142)]. The ring transformation of other 2(1H)-pyrimidinethiones was examined, and the results were summarized in Table 19. The possible mechanism for the ring transformation is speculated to be Dimroth type rearrangement as follows. (Scheme 27) Ammonia attacks at C-6 carbon of 36, and the resulting 293 undergoes the ring opening reaction to form the intermediate (102). By the attack of nitrogen originated from ammonia at thiocarbonyl carbon and subsequent elimination of hydrogen sulfide, stable 2-anilino-4,6-dimethylpyrimidine (97) is obtained. Next, 2(1H)-pyrimidinethione (36) was heated with methylamine as

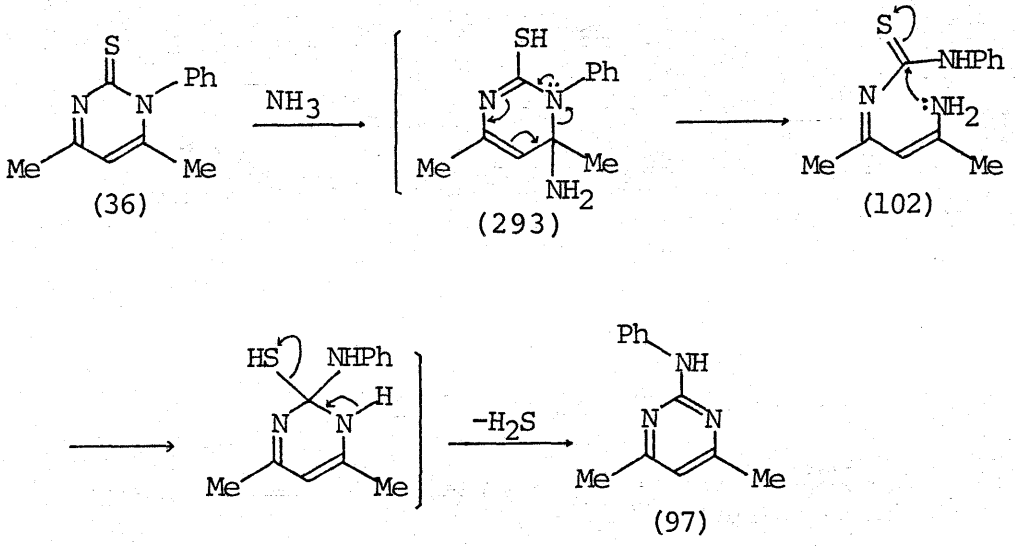
Table 19 2-(N-Substituted)aminopyrimidines



| Compd. No | $R^1$ | $R^2$ | $R^3$ | Product No | Mp[a] (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| 29 | Me | Me | Ph | 98 | 152-153[b] | 29 |
| 37 | p-$MeC_6H_4$ | Me | Me | 99 | 142-143 | 39 |
| 59 | Ph | Me | Ph | 100 | 112-113.5 | 42 |
| 62 | Ph | Me | p-$ClC_6H_4$ | 101 | 118-119 | 35 |

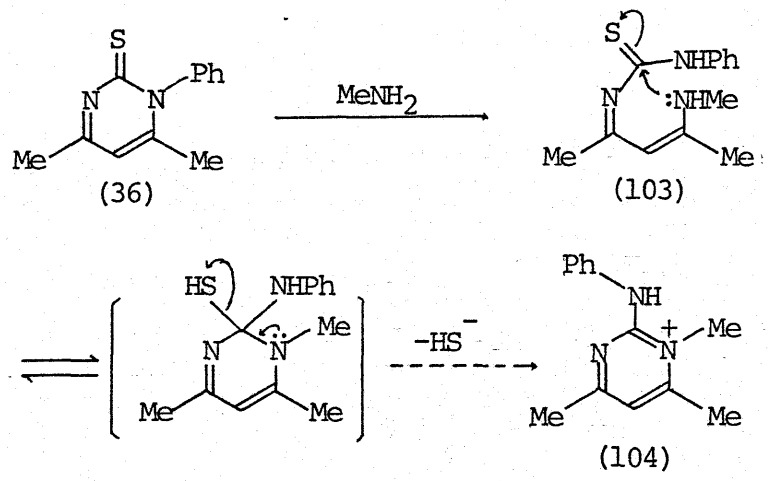
a) Recrystallized from benzene-hexane mixture.

b) Decomposition.



Scheme 27

a primary amine, which was expected to transform through the same reaction mechanism, but the expected product could not be obtained owing to the complex reaction. However, the compound 36 was stirred with methylamine at room temperature to give the ring opening product (103). (Scheme 28)



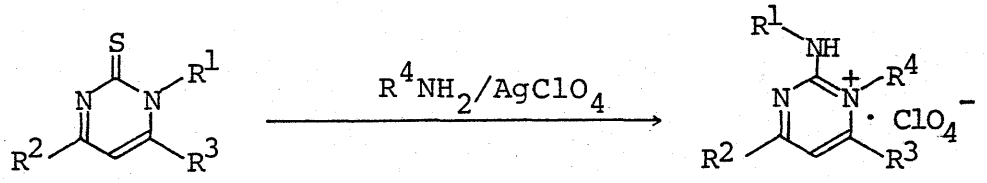

Scheme 28

So, the author tried to isolate the intermediate (104) as stable salt in the presence of counter ion. When 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) reacted with methylamine in the presence of barium perchlorate or sodium perchlorate, the product (mp 193-195 °C) was obtained. The formula of the product was found to be $C_{13}H_{16}ClN_3O_4$. The PMR spectrum displayed two methyl protons at δ 2.42 and 2.66, one olefinic proton at δ 7.01 ppm. Further, it exhibited a new signal at δ 3.88 ppm due to N-methyl protons. From these data, the product was determined to be 2-anilino-1,4,6-

trimethylpyrimidinium perchlorate (105). However, the yield of 105 was only 5%. It is supposed that the removal of the resulting hydrogen sulfide by the precipitation as metal sulfide raises the yield of 105. Actually, 2(1H)-pyrimidinethione (36) was treated with methylamine in the presence of silver perchlorate to afford the compound 105 (48% yield) and black precipitate. The latter was found to be silver sulfide ($Ag_2S$) from powder X-ray diffraction. Also, the compound 105 was obtained by the reaction of the ring opening product 104 with silver perchlorate in methanol. The ring transformation of other 2(1H)-pyrimidinethiones with primary amines in the presence of silver perchlorate was examined, and the results were summarized in Table 20. In the case of aromatic amines such as p-toluidine, the pyrimidinium perchlorates could not be obtained. It is attributed to the lower nucleophilicity and steric hindrance of aromatic amines.

Since Kröger [140] reported that 4-amino-1-methyl-2-methylaminopyrimidinium iodide was easily hydrolyzed to 1-methylcytosine. So, the conversion of the pyrimidinium perchlorate into 2(1H)-pyrimidinones was attempted. The pyrimidinium perchlorate 105 was hydrolyzed with concentrated hydrochloric acid at 160 °C to afford 1,4,6-trimethyl-2(1H)-pyrimidinone (4), which was identical with an authentic sample prepared from acetylacetone and N-methylurea[17]. The acid hydrolysis of other 2-(N-substituted)aminopyrimidinium

Table 20 2-(N-Substituted)aminopyrimidinium Perchlorates

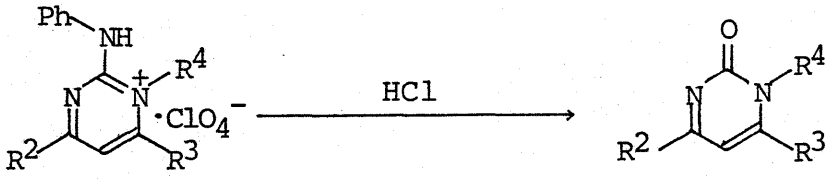



| Product No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Mp[a] (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| 105 | Ph | Me | Me | Me | 193-195 | 48 |
| 106 | Ph | Me | Me | Et | 201.5-202.5 | 28 |
| 107 | p-$MeC_6H_4$ | Me | Me | Me | 218.5-219.5 | 46 |
| 108 | p-$MeOC_6H_4$ | Me | Me | Me | 207-208 | 21 |
| 109 | Ph | Me | Ph | Me | 253-255 | 62 |
| 110 | Ph | Me | Ph | Et | 225-227 | 40 |
| 111 | Ph | Me | p-$MeC_6H_4$ | Me | 203.5-205 | 59 |
| 112 | Ph | Me | p-$MeOC_6H_4$ | Me | 219.5-220.5 | 72 |
| 113 | Ph | Me | p-$ClC_6H_4$ | Me | 216-216.5 | 39 |

a) Recrystallized from ethanol.

perchlorates was carried out, and the results were shown in Table 21.

Table 21 1,4,6-Trisubstituted 2(1H)-Pyrimidinones




| Product No | $R^2$ | $R^3$ | $R^4$ | Mp[a] (°C) | Yield (%) |
|---|---|---|---|---|---|
| 28 | Me | Ph | Me | 185-185.5 | 75 |
| 114 | Me | Ph | Et | 147-147.5 | 87 |
| 115 | Me | p-$MeOC_6H_4$ | Me | 140.5-141 | 39 |
| 116 | Me | p-$ClC_6H_4$ | Me | 121.5-122.5 | 68 |

a) Recrystallized from benzene-hexane mixture.

It is concluded that 1,4,6-trisubstituted 2(1H)-pyrimidinethiones undergo Dimroth type ring transformation with ammonia or alkyl amines in the presence of silver perchlorate to give 2-(N-substituted)aminopyrimidines or pyrimidinium perchlorates, respectively. Moreover, the pyrimidinium perchlorates are converted into 2(1H)-pyrimidinones in good yields by acid hydrolysis.

## III-3-2 The Reaction with Hydroxylamine[143)]

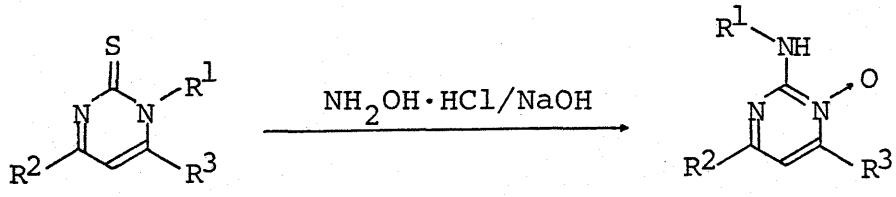
There have been many reviews on the synthesis of isoxazoles[10),144)] and pyrimidine N-oxides[145)]. Isoxazoles are also obtained by the ring transformation of pyrimidines[146)] and pyrimidine N-oxides[147)]. On the other hand, no attempts to prepare isoxazoles and pyrimidine N-oxides by the ring transformation of 2(1H)-pyrimidinethiones have been carried out, to the best of a knowledge. Further, the preparation of 2-(N-substituted)aminopyrimidine 1-oxides has not been reported, except for the preparation of 2,4,6-triaminopyrimidine N-oxides[148)]. In the previous section (III-3-1), it was found that 1-aryl-2(1H)-pyrimidinethiones underwent Dimroth type ring transformation with ammonia to give 2-(N-substituted)aminopyrimidines. On the basis of the speculated mechanism as shown in Scheme 27, it is expected that Dimroth type ring transformation occurs in not only ammonia but also hydroxylamine. Therefore, the author investigated Dimroth type ring transformation of 1-aryl-2(1H)-pyrimidinethiones with hydroxylamine.

When 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) was treated with hydroxylamine hydrochloride in the presence of sodium hydroxide, a product, mp 155.5-156 °C, was obtained. The product had the formula $C_{12}H_{13}N_3O$ and displayed strong bands at 3240 and 1240 $cm^{-1}$ due to N-H and N→O stretching in the IR spectrum. In section II-2, it was found that C-6

methyl protons of 1-aryl-2(1H)-pyrimidinethiones resonated at higher field by about 0.4 ppm than C-4 methyl protons due to the shielding effect of the aryl ring. By examination of the PMR spectrum, this shielding effect had disappeared in this reaction product, and C-4 and C-6 methyl protons showed sharp signals at δ 2.41 (s, 3H) and 2.52 (s, 3H). In addition, the CMR spectrum of the product still indicated the structure unit, Me-C(=)-CH=C(-)-Me. From these spectral data, the product was assigned to be 2-anilino-4,6-dimethylpyrimidine 1-oxide (117). The structure of 117 was also confirmed by chemical reaction. It is well known that pyrimidine N-oxides are easily deoxygenated with Raney nickel or phosphorus trichloride to give the corresponding pyrimidines[149]. Thus, the compound 117 was treated with Raney nickel to afford 2-anilino-4,6-dimethylpyrimidine (97), which was identical (spectral data and mixed melting point) with an authentic sample prepared from 2-chloro-4,6-dimethylpyrimidine (12) and aniline[70),142]. The Dimroth type ring transformation of other 2(1H)-pyrimidinethiones was examined, and the results were summarized in Table 22.

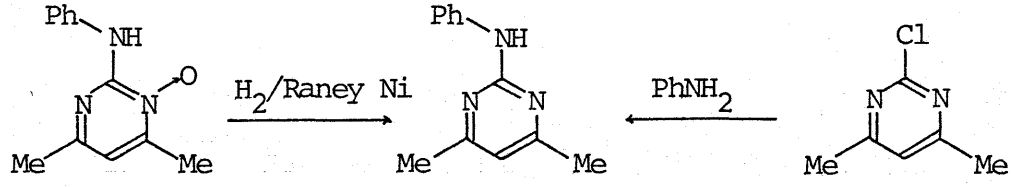
On the other hand, 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) reacted with hydroxylamine in the manner described above to give 3,5-dimethylisoxazole (125) and N-phenylurea. The former compound was identical with an authentic sample obtained from acetylacetone and hydroxylamine hydrochloride[150]. 4-Methyl-1,6-diphenyl-

Table 22 2-(N-Substituted)aminopyrimidine 1-Oxides



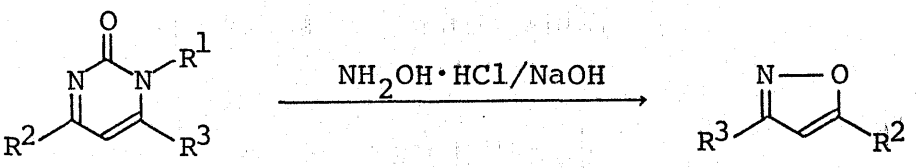

| Compd. No | $R^1$ | $R^2$ | $R^3$ | Product No | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| 36 | Ph | Me | Me | 117 | 155.5-156[a] | 80 |
| 22 | Me | Me | Me | 118 | 143.5-144[a] | 30 |
| 37 | p-$MeC_6H_4$ | Me | Me | 119 | 199-200[b] | 39 |
| 48 | o-$MeC_6H_4$ | Me | Me | 120 | 110-111[a] | 28 |
| 50 | o-$EtC_6H_4$ | Me | Me | 121 | 108-110[a] | 43 |
| 59 | Ph | Me | Ph | 122 | 176-176.5[a] | 30 |
| 60 | Ph | Me | p-$MeC_6H_4$ | 123 | 157-158[a] | 44 |
| 62 | Ph | Me | p-$ClC_6H_4$ | 124 | 189-190[c] | 35 |

a) Recrystallized from benzene-hexane mixture.
b) From benzene. c) From ethanol.




(117) (97) (12)

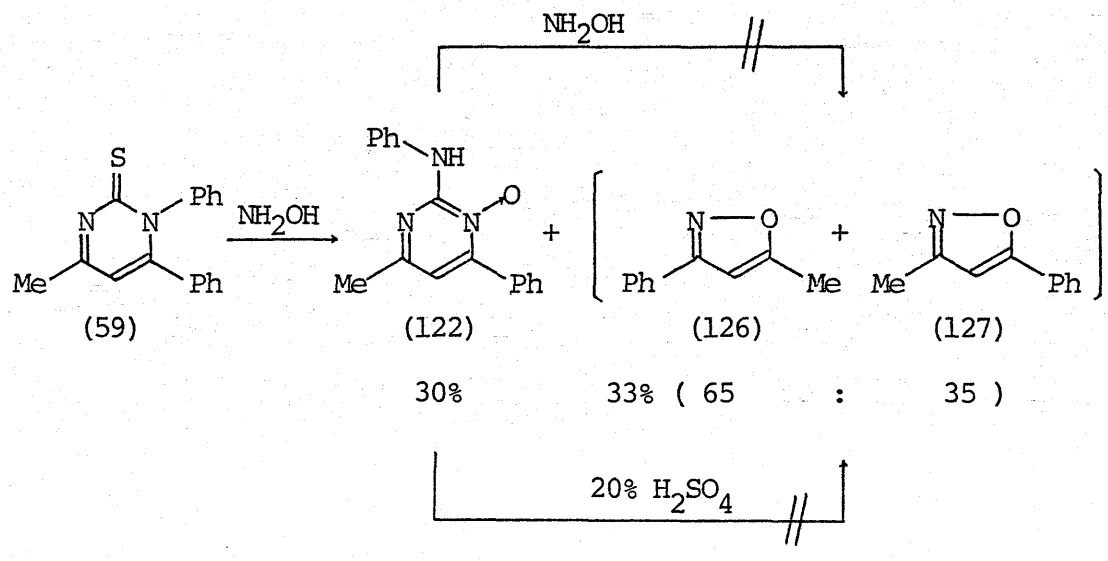
Table 23 3,5-Disubstituted Isoxazoles




| Compd. No | $R^1$ | $R^2$ | $R^3$ | Product No | Formula | Yield (%) | Mp[or Bp] (°C) | Lit. Mp[or Bp] (°C) |
|---|---|---|---|---|---|---|---|---|
| 32 | Ph | Me | Me | 125 | $C_5H_7NO$ | 80 | [139-140.5] | [136-140][150] |
| 54 | Ph | Me | Ph | 126 | $C_{10}H_9NO$ | 71 | 67-68 | 65[151] |
| 55 | Ph | Ph | Me | 127 | $C_{10}H_9NO$ | 66 | 42-44 | 42[151] |
| 58 | Ph | p-$ClC_6H_4$ | Me | 128 | $C_{10}H_8NOCl$ | 75 | 90-91 | 91-92[152] |
| 31 | p-$MeC_6H_4$ | Ph | Ph | 129 | $C_{15}H_{11}NO$ | 80 | 142-143 | 141-142.5[153] |

2(1H)-pyrimidinone (54) also underwent the ring transformation to give only 5-methyl-3-phenylisoxazole (126) in 71% yield. The ring transformation of other 2(1H)-pyrimidinones was carried out, and the results were summarized in Table 23.

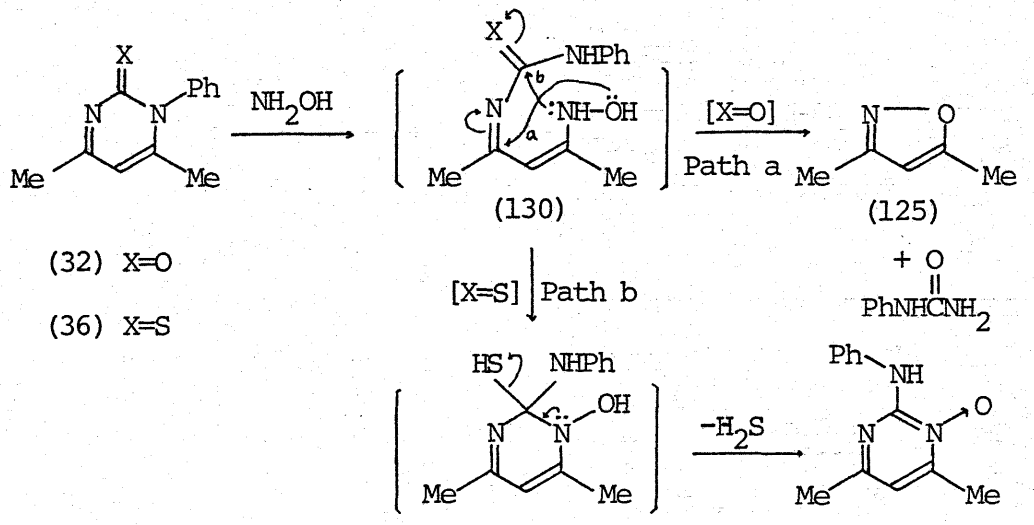
In the case of 4-methyl-1,6-diphenyl-2(1H)-pyrimidinethione (59), pyrimidine 1-oxide (122) and a mixture of isoxazoles (126 and 127, 33%) were obtained. Yamanaka et al. reported that pyrimidine N-oxides were converted into isoxazoles in good yields by acid hydrolysis with 20% sulfuric acid[154]. The conversion of 122 into 126 and 127 did not occur even prolonged reaction and acid hydrolysis with 20% sulfuric acid. (Scheme 29)




Scheme 29

A possible mechanism for the ring transformation of 2(1H)-pyrimidinones is speculated as follows. (Scheme 30)
The attack of hydroxylamine on C-6 carbon of 32 or 36

and subsequent the ring opening reaction form the intermediate (130). In the case of 2(1H)-pyrimidinone (32), oxygen originated from hydroxylamine attacks β-carbon of 130 to afford 3,5-dimethylisoxazole (125) and N-phenylurea. (Path a) In the case of 2(1H)-pyrimidinethione (36), the intermediate 130 cyclizes and subsequently eliminates hydrogen sulfide to yield 2-anilino-4,6-dimethylpyrimidine 1-oxide (117). (Path b)

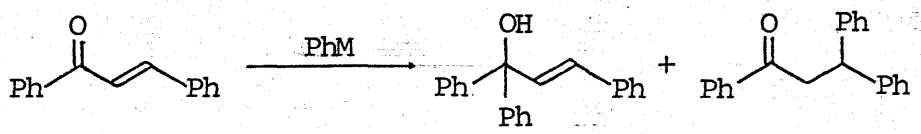



Scheme 30

It is concluded that 1,4,6-trisubstituted 2(1H)-pyrimidinethiones undergo Dimroth type ring transformation with hydroxylamine to afford mainly a new type of 2-(N-substituted)aminopyrimidine 1-oxides. Further it is found that 1,4,6-trisubstituted 2(1H)-pyrimidinones undergo ring transformation to give 3,5-disubstituted isoxazoles in high yields.

## III-3-3 The Reaction with Organometallic Reagents[155)]

Many papers have been reported on the preparation of dihydro-2(1H)-pyrimidinones. (See INTRODUCTION) On the other hand, few papers concerning the preparation of dihydro-2(1H)-pyrimidinones by the reaction of 2(1H)-pyrimidinones with nucleophiles have been reported[91)-93)]. By the result of INDO calculation, nucleophilic attack could be expected to take place on C-2, C-4 and C-6 carbon of the pyrimidine ring. Meanwhile Hauser reported that phenyllithium reacted with enone such as benzalacetophenone (131) to yield predominantly 1,2-addition product (132), and phenylmagnesium bromide gave exclusively 1,4-addition product (133)[156)]. (Scheme 31)



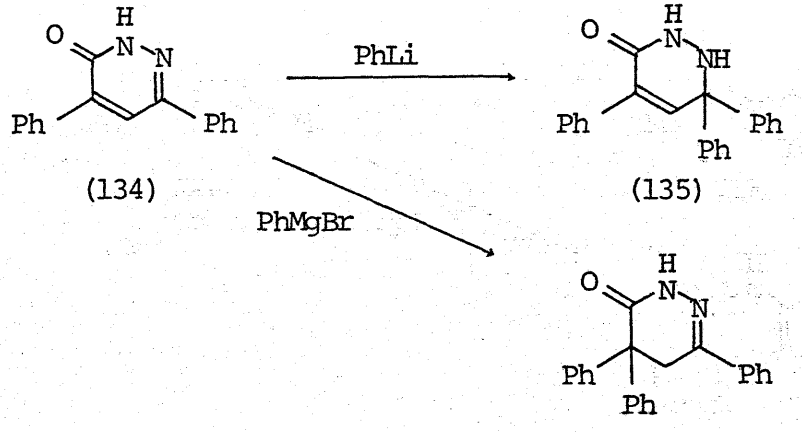

(131) (132) (133)

| | | |
|---|---|---|
| M = Li | 75% | 14% |
| M = MgBr | —— | 94% |

Scheme 31

Recently the different regioselective behavior of organolithium and organomagnesium reagents toward pyridazine derivatives was reported by Fateen[157),158)]. 4,6-Diphenyl-

3(2H)-pyridazinone (134), for example, reacted with phenyllithium to give 1,6-dihydro-4,6,6-triphenyl-3(2H)-pyridazinone (135). On the contrary, when the compound 134 was allowed to react with phenylmagnesium bromide, 4,5-dihydro-4,4,6-triphenyl-3(2H)-pyridazinone (136) was obtained. (Scheme 32)




(134) (135) (136)

Scheme 32

Therefore, the author investigated the regioselective preparation of dihydro-2(1H)-pyrimidinones with organometallic reagents such as Grignard and organolithium reagents.

The reaction of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) with methylmagnesium iodide (MeMgI) yielded two products, mp 191-192 °C (compound A) and mp 163 °C (compound B). Both compounds had the same formula, $C_{13}H_{16}N_2O$, from elemental analysis. Compound A showed the following spectral data. The IR spectrum displayed bands at 3200 and 1660 $cm^{-1}$ due to N-H and C=O stretching, respectively. The PMR

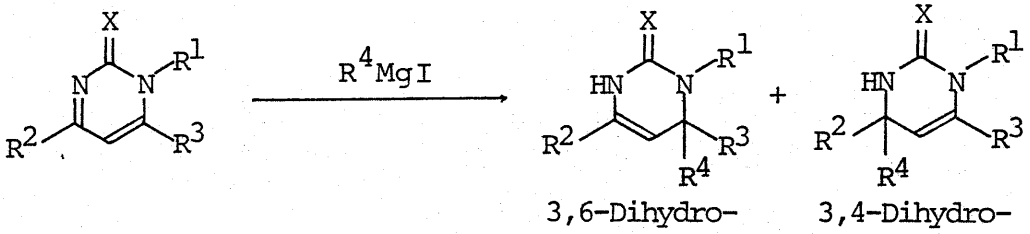
spectrum had a singlet at δ 1.18 (6H) and a doublet at δ 1.70 ppm (3H, J=0.6 Hz) attributed to the allyl coupling of methyl protons with an olefinic proton at C-5 position of the pyrimidine ring. On the contrary, the IR spectrum showed absorption bands at 3200 (N-H) and 1660 $cm^{-1}$ (C=O), and the PMR spectrum exhibited signals at δ 1.30 (s, 6H) and 1.53 ppm (d, 3H, J=0.6 Hz) in the compound B. From these spectral data, compound A and B were assumed to be structurally isomeric with each other, and compound B was found to be 3,4-dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (138) by comparison with an authentic sample (mp 162-164 °C) obtained from the reaction of 1,1-dimethyl-3-oxobutyl isocyanate with aniline[27]. It appears that compound 137 is formed by the attack of the methyl Grignard at the C-4 position of the pyrimidine ring. Therefore, compound A was assigned the structure 3,6-dihydro-4,6,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (137) which was formed by the attack of the methyl Grignard at the C-6 position. The total yield of 137 and 138 was 29% in the ratio of 95 : 5. 2(1H)-Pyrimidinone (32) also reacted with methyllithium (MeLi) to give two products 137 and 138 in 65% yield, but the ratio was 15 : 85. (Table 24 and 25)
When 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) was treated with MeMgI and MeLi to afford a mixture of two products, 144 and 145, in 62 and 43% yield, respectively. The structures of 144 and 145 were determined from the fact

that the chemical shifts of the geminal dimethyl and allylic methyl protons were very similar to those of compounds 137 and 138, respectively. Further, the compound 145 was found to be identical with an authentic sample of 3,4-dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinethione (145) obtained from the reaction of 2-methyl-2-thiocyanatopentan-4-one with aniline[29]. Similarly, the reaction of 2(1H)-pyrimidinones with various alkyl Grignards and alkyl-lithium reagents was examined, and the results were summarized in Table 24 and 25.

These results suggest that the bulkiness of the alkyl group of the Grignard reagent has a large influence on the ratio of the 3,6-dihydro-2(1H)-pyrimidinones 137, 139, 142 to the 3,4-dihydro-2(1H)-pyrimidinones 138, 140, 141, 143, but not on the ratio of the 3,6-dihydro-2(1H)-pyrimidinethiones 144, 146, 148, 150 to the 3,4-dihydro-2(1H)-pyrimidinethiones 145, 147, 149, 151.

6-Methyl-1,4-diphenyl-2(1H)-pyrimidinone (54) reacted with MeMgI to give only 3,6-dihydro-6,6-dimethyl-1,4-diphenyl-2(1H)-pyrimidinone (156) in 67% yield, while 4-methyl-1,6-diphenyl-2(1H)-pyrimidinethione (59) with MeMgI gave only 3,4-dihydro-4,4-dimethyl-1,6-diphenyl-2(1H)-pyrimidinethione (157) in 82% yield. (Table 24) Finally, the author examined the reaction of MeMgI or MeLi with 1-phenyl-2(1H)-pyrimidinone (23), which has no substituent at C-4 and C-6 position of the pyrimidine ring. The compound 23

Table 24 The Reaction with Grignard Reagents

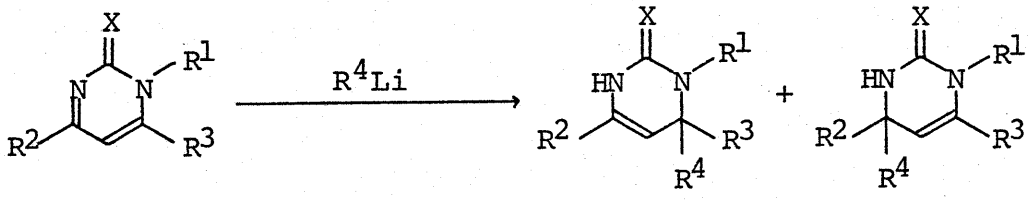



| Compd. No | $R^4$ | Product No | Yield (%) | Ratio (3,6- : 3,4-) |
|---|---|---|---|---|
| 32 | Me | 137 and 138 | 29 | 95 : 5 |
| 32 | Et | 139 and 140 | 20 | 50 : 50 |
| 32 | $Pr^i$ | 141 | 19 | 0 : 100 |
| 32 | $Bu^t$ a) | 142 and 143 | 59 | 20 : 80 |
| 36 | Me | 144 and 145 | 62 | 70 : 30 |
| 36 | Et | 146 and 147 | 83 | 60 : 40 |
| 36 | $Pr^i$ | 148 and 149 | 48 | 75 : 25 |
| 36 | $Bu^t$ a) | 150 and 151 | 75 | 30 : 70 |
| 20 | Ph-C≡C b) | 152 | 70 | 100 : 0 |
| 23 | Me | 153 | 59 | 100 : 0 |
| 33 | Me | 154 and 155 | 46 | 95 : 5 |
| 54 | Me | 156 | 67 | 100 : 0 |
| 59 | Me | 157 | 82 | 0 : 100 |

a) t-Butylmagnesium chloride.

b) Phenylethynylmagnesium bromide.

Table 25 The Reaction with Organolithium Reagents




3,6-Dihydro- 3,4-Dihydro-

| Compd. No | $R^4$ | Product No | Yield (%) | Ratio (3,6- : 3,4-) |
|---|---|---|---|---|
| 32 | Me | 137 and 138 | 65 | 15 : 85 |
| 32 | Et | 139 and 140 | 42 | 10 : 90 |
| 32 | $Pr^i$ | 141 | 12 | 0 : 100 |
| 36 | Me | 144 and 145 | 43 | 35 : 65 |
| 36 | Et | 147 | 42 | 0 : 100 |
| 36 | $Pr^i$ | 149 | 10 | 0 : 100 |
| 33 | Me | 154 and 155 | 56 | 5 : 95 |
| 23 | Me | 158 | 88 | 0 : 100 |

reacted with MeMgI to yield only 3,6-dihydro-6-methyl-1-phenyl-2(1H)-pyrimidinone (153) in 59% yield. On the other hand, the compound 23 also reacted with MeLi to give exclusively 3,4-dihydro-4-methyl-1-phenyl-2(1H)-pyrimidinone (158) in 88% yield. (Table 24 and 25)

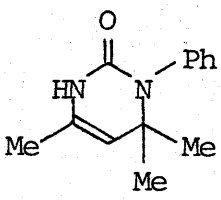
It is thus possible to prepare regioselectively 3,6-dihydro- and 3,4-dihydro-2(1H)-pyrimidinones with the appropriate organometallic reagents. Further, it is concluded that alkyl Grignards attack at C-6 position in preference to C-4 position of the pyrimidine ring, while alkyl-lithium reagents attack C-4 position.

## III-3-4 The Reaction with Metal Hydride Complexes[159)]

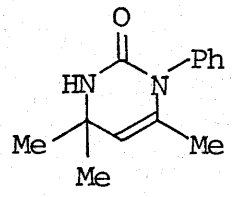
In the previous section (III-3-3), the author discussed on the regioselective preparation of dihydro-2(1H)-pyrimidinones with organometallic reagents such as Grignard and organolithium reagents[155)]. The dihydro- and tetrahydro-2(1H)-pyrimidinones are quite useful intermediates in the synthesis of 1,3-diamines[11)] and thiazines[12)]. Meanwhile the attempt to prepare reduced 2(1H)-pyrimidinones has been carried out under drastic conditions with palladium[11)], rhodium, Raney nickel[26)] and platinum[160-163)] as catalyst. From these points of view, it seemed to be very important to control the reduction of 2(1H)-pyrimidinones into either dihyro- or tetrahydro-2(1H)-pyrimidinones. To the best of a knowledge, the reduction of 2(1H)-pyrimidinones with metal hydride complexes has not previously been reported. Therefore, the author investigated the regioselective preparation of dihydro- and tetrahydro-2(1H)-pyrimidinones by the controlled reduction of 2(1H)-pyrimidinones with metal hydride complexes, such as sodium borohydride and lithium aluminum hydride, under various conditions.

When 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) was treated with sodium borohydride ($NaBH_4$), three products were obtained: compound A, mp 134-135 °C; compound B, mp 119-120 °C; and compound C, mp 178-179 °C. The microanalytical results for products A and B were consistent with

their formulation as $C_{12}H_{14}N_2O$. The spectral characteristics were as follows: compound A, IR 3200 (N-H) and 1660 $cm^{-1}$ (C=O) and PMR δ 1.13 (d, 3H, J=6.0 Hz) and 1.73 (s, 3H); compound B, IR 3220 (N-H) and 1660 $cm^{-1}$ (C=O) and PMR δ 1.27 (d, 3H, J=6.0 Hz) and 1.52 (s, 3H). On the basis of these spectral data, compounds A and B were assumed to be structurally isomeric. Moreover, the comparison of the spectral characteristics with those of compound 137 and 138[155] allowed A and B to be assigned the structures 3,6-dihydro-4,6-dimethyl-1-phenyl- (159) and 3,4-dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (160), respectively.



(137)

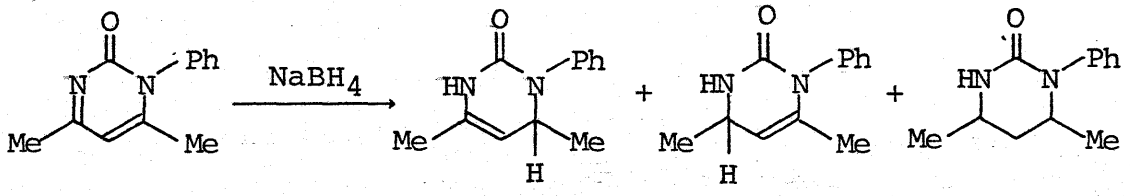


(138)

These structural assigments were supported by UV spectral evidence. Compound C gave microanalytical results consistent with its formulation as $C_{12}H_{16}N_2O$ and showed the following spectral characteristics: IR 3200 (N-H) and 1650 $cm^{-1}$ (C=O) and PMR δ 0.93 (d, 3H, J=6.0 Hz) and 1.13 (d, 3H, J=6.0 Hz). From these results compound C was deduced to be tetrahydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (161).

The ratio of three products (159) : (160) : (161) was sensitive to the reaction conditions changing from 37 : 13 : 50 with methanol as the solvent, to 0 : 4 : 96 with ethanol.

Since it is known that $NaBH_4$ reacts with methanol, at an appreciable rate, to form methyl borate, but is fairly stable in ethanol[164], and that the formation of compound 161 was inhibited in methanol, the author assumes that methyl borate inhibited the further reduction of 159 to 161.




(32) (159) (160) (161)

| | | | | | | |
|---|---|---|---|---|---|---|
| in MeOH | 37 | : | 13 | : | 50 |
| in EtOH | 0 | : | 4 | : | 96 |

* Determined by LPC.

$$NaBH_4 + 4MeOH \longrightarrow B(OMe)_3 + NaOMe + 4H_2$$

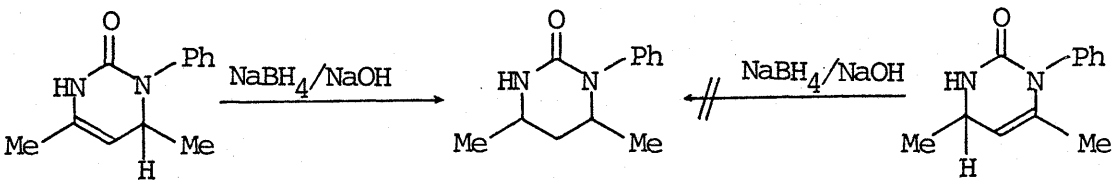
Further experimentals also indicated that the formation of methyl borate from $NaBH_4$ could be retarded when sodium hydroxide was added to the methanol. Therefore, the addition of methyl borate or sodium hydroxide changed the ratio (161)/[(159) + 160)], and the results were listed in Table 26. Tetrahydrofuran was used as a solvent in order to suppress the decomposition of $NaBH_4$. The yields of compounds 159 and 160 increased with an increase of methyl borate and decreased with an increase of sodium hydroxide. Moreover,

Table 26

| [ 32 : $NaBH_4$ : $B(OMe)_3$ : NaOH ] | | | | Solvent[a] | Tetrahydro(161)[b] / Dihydro(159+160) |
|---|---|---|---|---|---|
| 1 | 2 | 5 | 0 | A | 0.18 |
| 1 | 1 | 10 | 0 | A | 0.16 |
| 1 | 1 | 5 | 0 | A | 0.17 |
| 1 | 1 | 2 | 0 | A | 0.24 |
| 1 | 1 | 1 | 0 | A | 0.42 |
| 1 | 1 | 0 | 0 | B | 1.44 |
| 1 | 1 | 0 | 0.5 | B | 3.14 |
| 1 | 1 | 0 | 1 | B | 4.55 |
| 1 | 1 | 0 | 2 | B | 4.76 |
| 1 | 1 | 0 | 5 | B | 5.56 |
| 1 | 1 | 0 | 10 | B | 7.69 |

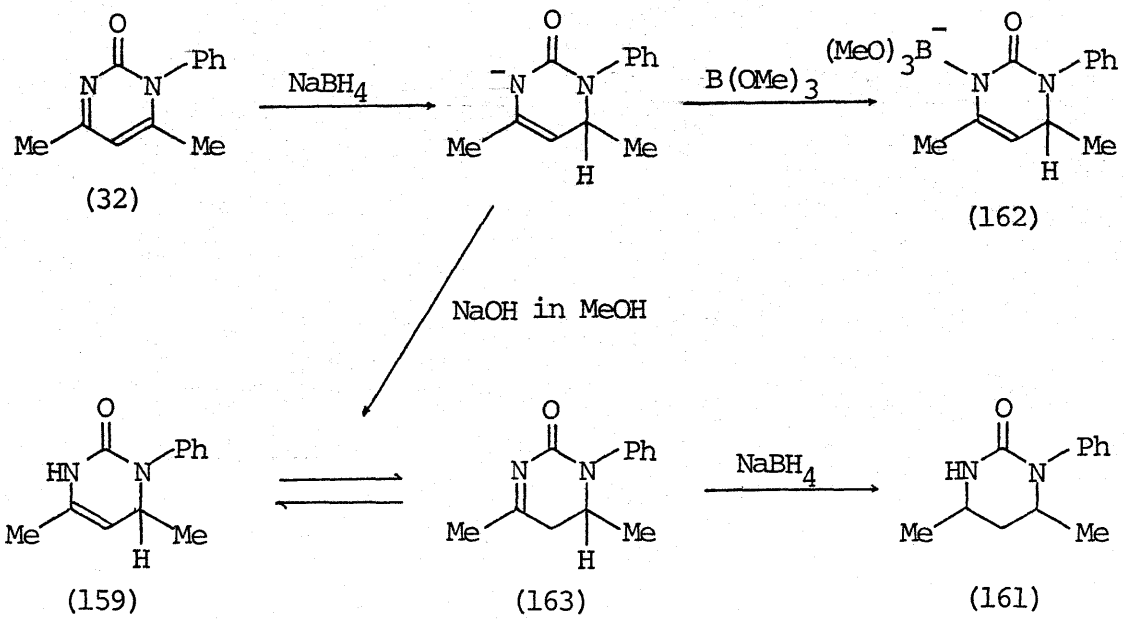
a) A=Tetrahydrofuran, B=Methanol.

b) Stirring for 4 hr at room temperature.
Determined by LPC.




(159) (161) (160)

it was ascertained that 3,6-dihyro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (159) was further reduced with $NaBH_4$ in the presence of sodium hydroxide, while the isomeric 3,4-dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (160) was not reduced under the same reaction. (Table 26) This difference may be attributed to the absence or presence of imine-enamine tautomerization. On the basis of the above results, the mechanism for reduction with $NaBH_4$ is speculated as follows. (Scheme 33)




Scheme 33

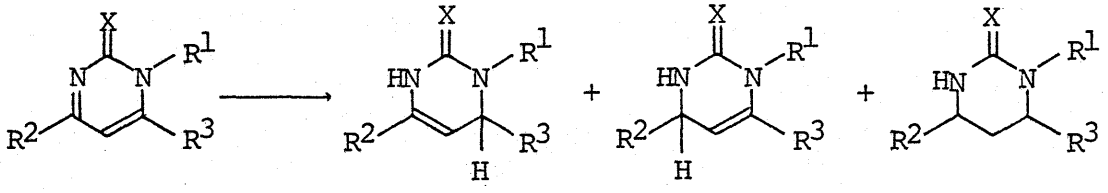
First the compound 32 is reduced two kinds of dihydro-2(1H)-pyrimidinones (159 and 160). By addition of methyl borate, the proton of N-3 nitrogen of the compound 159 should be

replaced with boron and the resulting complex molecule (162) should not be tautomerized because of the formation of the strong boron-nitrogen bond. On the other hand, if a base such as sodium hydroxide is present, the formation of the boron-nitrogen bond is disturbed and the tautomerization of enamine-imine is promoted. Tetrahydro-2(1H)-pyrimidinone (161) is obtained by further reduction with $NaBH_4$ through the imino form (163).

The reaction of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) with $NaBH_4$ was carried out in the same manner described above, and the results were shown in Table 27. 6-Methyl-1,4-diphenyl-2(1H)-pyrimidinone (54) was reduced with $NaBH_4$ or lithium aluminum hydride ($LiAlH_4$) to afford only 3,6-dihydro-6-methyl-1,4-diphenyl-2(1H)-pyrimidinone (167). Whereas 4-methyl-1,6-diphenyl-2(1H)-pyrimidinone (55) and the corresponding 2(1H)-pyrimidinethione (59) reacted with $LiAlH_4$ to give exclusively 3,4-dihydro-4-methyl-1,6-diphenyl-2(1H)-pyrimidinone (168) and -thione (170), respectively. (Table 27) These results suggest that the steric hindrance of the substituents at N-1, C-4, and C-6 position of the pyrimidine ring has a large influence on the reaction with $NaBH_4$ or $LiAlH_4$.

Since Marshall and Johnson[165] and Gribble et al.[166] have reported that enamines can be reduced by $NaBH_4$ in acetic acid, the author examined the behavior of 2(1H)-pyrimidinones with $NaBH_4$ in acetic acid. The results were summarized in

Table 27 The Reaction with $NaBH_4$ and $LiAlH_4$



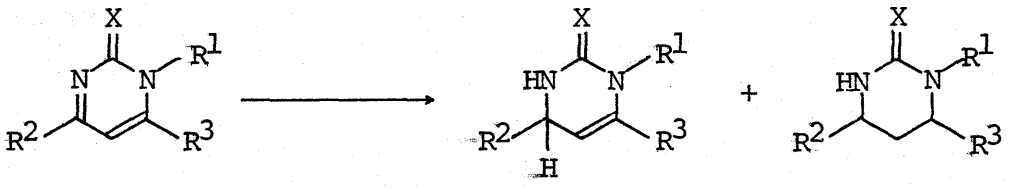
3,6-Dihydro- 3,4-Dihydro- Tetrahydro-

| Compd. No | Method[a] | Product No | Yield[b] (3,6-, %) | (3,4-, %) | (Tetra., %) |
|---|---|---|---|---|---|
| 32 | A | 159 | 90 | 0 | 0 |
| 32 | B | 161 | 0 | 0 | 91 |
| 32 | C | 160 and 161 | 0 | 31 | 52 |
| 32 | D | 159 and 160 | 28 | 65 | 0[c] |
| 36 | A | 164 | 85 | 0 | 0 |
| 36 | B | 166 | 0 | 0 | 84 |
| 36 | C | 165 and 166 | 0 | 30 | 45 |
| 36 | D | 164 and 165 | 45 | 45 | 0[c] |
| 54 | D | 167 | 85 | 0 | 0 |
| 54 | E | 167 | 79 | 0 | 0 |
| 55 | D | 168 | 0 | 71 | 0 |
| 55 | E | 169 and 168 | 19 | 77 | 0 |
| 59 | D | 170 | 0 | 90 | 0 |
| 59 | E | 171 and 170 | 57 | 38 | 0[c] |

a) See experimental section. b) Isolated Yield.

c) Determined by PMR spectroscopy.

Table 28 The Reaction with $NaBH_4$ in Acetic Acid[a)]




3,4-Dihydro- Tetrahydro-

| Compd. No | Product No | Yield (3,4-Dihydro-,%) | (Tetrahydro-,%) |
|---|---|---|---|
| 32 | 161 | 0 | 86 |
| 36 | 166 | 0 | 85 |
| 26 | 172 | 0 | 87 |
| 28 | 173 | 0 | 96 |
| 30 | 174 | 0 | 93 |
| 33 | 175 | 0 | 95 |
| 34 | 176 | 0 | 94 |
| 35 | 177 | 0 | 94 |
| 54 | 178 | 0 | 83 |
| 31 | 179 and 180 | 34 | 55 |
| 23 | 181 and 182 | 26 | 48 |
| 25 | 183 and 184 | 19 | 74 |
| 27 | 185 and 186 | 68 | 23 |
| 59 | 170 and 187 | 80 | 8 |

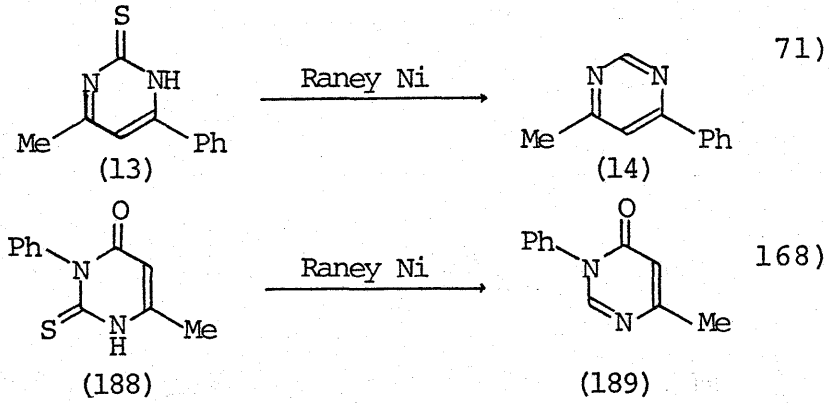
a) The reaction was carried out according to the method F. (See experimental section)

Table 28. The compounds gave either tetrahydro-derivatives exclusively or mixtures of the dihydro- and tetrahydro-derivatives. Further, in this reaction 3,6-dihydro-2(1H)-pyrimidinones could not be obtained. There is no simple correlation between the results and the steric effects of substituents at N-1, C-4, and C-6 position in the pyrimidine ring.

It is concluded that the regioselective preparation of 3,4- and 3,6-dihydro-, and tetrahydro-2(1H)-pyrimidinones is achieved by the controlled reduction of the corresponding 2(1H)-pyrimidinones using $NaBH_4$ and $LiAlH_4$ under a variety of conditions.

## III-4 The Desulfuration with Raney Nickel

Raney nickel has been widely applied for the desulfuration of heterocyclic thioamides and related compounds[167]. For example, 4-methyl-6-phenyl-2(1H)-pyrimidinethione (13) and 6-methyl-3-phenyl-2-thiouracil (188) are treated with Raney nickel to give 4-methyl-6-phenylpyrimidine (14) and 6-methyl-3-phenyl-4(3H)-pyrimidinone (189)[71),168], respectively. (Scheme 34)



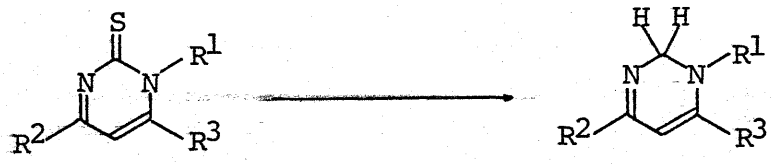

Scheme 34

Therefore, the author investigated the desulfuration of 2(1H)-pyrimidinethiones with Raney nickel.

When 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36) was warmed with Raney nickel in methanol at 60 °C for 3 hr, the simple product could not obtain owing to the dirty reaction. The compound 36 was treated with Raney nickel at room temperature under hydrogen atmosphere to give a product which had the formula $C_{12}H_{14}N_2$. The PMR spectrum showed

two methyl protons at δ 1.83 (s, 3H) and 2.02 (s, 3H) and an olefinic proton at δ 5.37 ppm (s, 1H). Further, it exhibited a new signal at δ 4.98 ppm (s, 2H) due to methylene protons of the pyrimidine ring. From these data, the product was assigned to be 1,2-dihydro-4,6-dimethyl-1-phenylpyrimidine (190). The desulfuration of other 2(1H)-pyrimidinethiones was carried out, and the results were listed in Table 29.

Table 29 The Desulfuration with Raney Nickel



| Compd. No | $R^1$ | $R^2$ | $R^3$ | Product No | Yield (%) |
|---|---|---|---|---|---|
| 36 | Ph | Me | Me | 190 | 27 |
| 29 | Me | Me | Ph | 191 | 66 |
| 37 | p-$MeC_6H_4$ | Me | Me | 192 | 36 |
| 193 | p-$MeOC_6H_4$ | Me | Me | 194 | 34 |

In conclusion, 2(1H)-pyrimidinethiones are desulfurized with Raney nickel to afford 1,2-dihydropyrimidines.

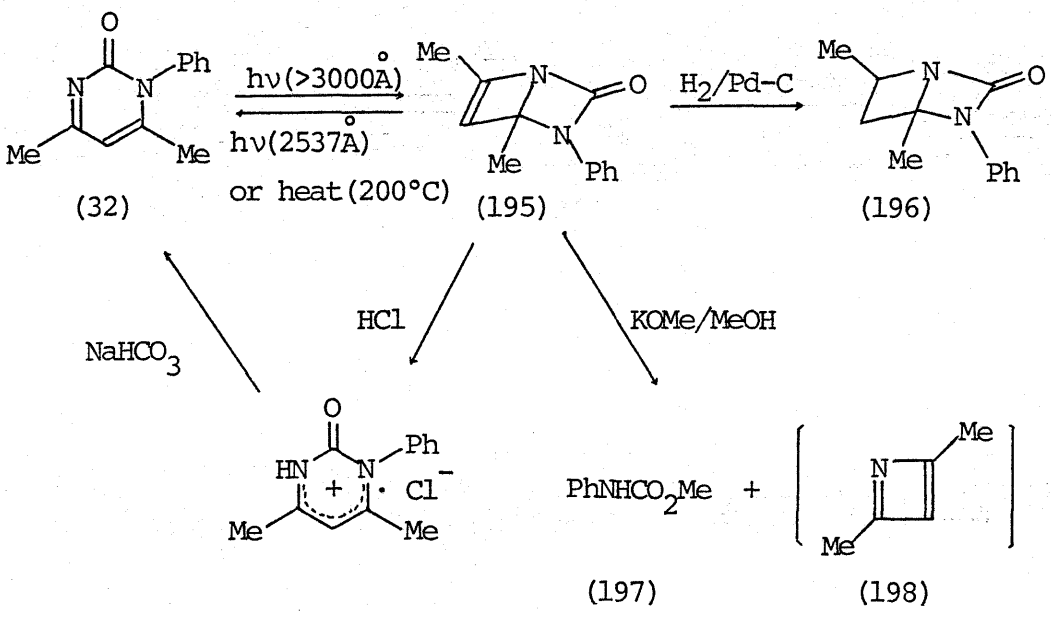
## III-5 The Photochemical Reaction[169)-171)]

The phtochemical reaction of nucleic acid bases and their related compounds is a significant area for understanding the photo-reactivity of nucleic acids and the photo-mutation *in vivo*, and this area has been extensively studied[94)-96)]. However, little attention has been paid to the photochemical reaction of 2(1H)-pyrimidinones which are very similar to the pyrimidine bases. Recently Pfoertner reported[97)] that π-π* excitation of 4,6-dimethyl-2(1H)-pyrimidinone in methanol led to an addition product, 3,4-dihydro-4-hydroxymethyl-4,6-dimethyl-2(1H)-pyrimidinone, while in 2-propanol a dihydrodimer, 4,4',6,6'-tetramethyl-3,3',4,4'-tetrahydro-1H,1'H-[4,4'-bipyrimidine]-2,2'-dione, was formed.

As a part of studying the chemical reactions, the author investigated the photochemical reaction of 2(1H)-pyrimidinones.

When 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone [(32); $\lambda_{max.}^{EtOH}$ 210 (ε 2.23 x $10^4$) and 304 nm (9.5 x $10^3$)] in benzene was irradiated in a Pyrex vessel with a high-pressure mercury lamp under an argon atmosphere for 15 hr at room temperature, 3-phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo-[2.2.0]hex-5-ene (195), an isomer of the compound 32, was obtained in 67% yield. The structure of 195 was determined on the basis of the physical data and elemental analysis.

The mass spectrum revealed a base peak at m/e 200 and major peaks at m/e 119, 81, and 80, corresponding to phenyl isocyanate, 2,4-dimethyl-1-azacyclobutadiene, and 2,4-dimethyl-1-azacyclobutadienyl cation fragments, respectively. The IR absorption showed at 1760 $cm^{-1}$ characteristic of the fused urea carbonyl and at 1640 $cm^{-1}$ due to the fused cyclobutene double bond, respectively. The PMR spectrum showed a singlet at δ 1.83(3H), a doublet at δ 2.08(3H,J= 1.5 Hz), and a quartet at δ 6.00 ppm (1H, J=1.5 Hz), assignable to C-4 methyl, C-6 methyl, and an olefinic protons, respectively, in addition to aromatic protons. Further, the structure of the photo-isomer 195 was confirmed by chemical reactions. (Scheme 35).

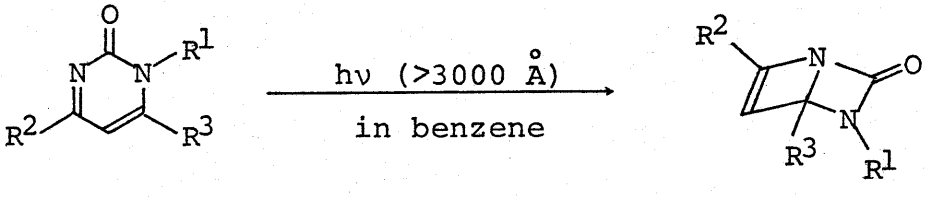



Scheme 35

The hydrogenation over palladium-charcoal of the photo-isomer 195 gave 3-phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo-[2.2.0]hexane (196) in 60% yield. The photo-isomer 195 was very stable at room temperature. However, the thermolysis of molten (195) in a sealed tube at 200 °C or irradiation of 195 in methanol through quartz with 2537 Å radiation causes reversion to the starting 2(1H)-pyrimidinone (32) in almost quantitative yield. Furthermore, the photo-isomer 195 was treated with potassium methoxide in methanol to give methyl N-phenylcarbamate (197) and unidentified products from 2,4-dimethyl-1-azacyclobutadiene (198). Treatment of 32 with potassium methoxide in methanol did not give any products, and 32 was quantitatively recovered. The starting 2(1H)-pyrimidinone (32) was obtained when 195 was treated with hydrochloric acid, followed by sodium hydrogen carbonate. Similarly the irradiation of other 2(1H)-pyrimidinones under the same conditions gave the corresponding 2-oxo-1,3-diazabicyclo[2.2.0]hex-5-enes in 14-85% yield. (Table 30) These photo-isomers were also stable at room temperature and stored indefinitely. In the case of (199) and (207), they were converted back to the starting 2(1H)-pyrimidinones (4) and (47) during purification by distillation (125 °C/5 mmHg) or recrystallization (benzene-hexane mixture).

The formation of 3,4,6-trisubstituted 2-oxo-1,3-diaza-bicyclo[2.2.0]hex-5-enes can be explained in terms of a photochemical electrocyclization reaction. Similar reactions

Table 30 The Photochemical Reaction of 2(1H)-Pyrimidinones




| Compd. No | Time (hr) | Product No | Mp(°C) [or Bp] | Yield (%) | Recovered (%) |
|---|---|---|---|---|---|
| 32 | 15 | 195 | 64.5-66.0 | 67 | 10 |
| | | | | (0.52)[a] | |
| 32 | 2 | 195 | | 61[b] | 39[b] |
| 4 | 15 | 199 | [125°C/5 mmHg] | 33 | 30 |
| | | | | (0.79)[a] | |
| 4 | 2 | 199 | | 93[b] | 7[b] |
| 40 | 15 | 200 | 74.5-75.5 | 85 | 13 |
| 41 | 12 | 201 | [120°C/5 mmHg] | 55 | 13 |
| 42 | 12 | 202 | [112°C/2 mmHg] | 50 | 17 |
| 43 | 10 | 203 | [125°C/5 mmHg] | 43 | 15 |
| 45 | 15 | 204 | [125°C/5 mmHg] | 66 | 25 |
| 33 | 15 | 205 | 62-63 | 57 | 30 |
| 34 | 15 | 206 | 66-67 | 33 | 25 |
| 47 | 45 | 207 | 56.5-58.0 | 23 | 35 |
| 28 | 45 | 208 | 133(decomp.) | 14 | 63 |

a) Quantum yield. b) Determined by GLC.

of pyridazin-2-one[172], 2-pyrone[173], and 2-pyridone derivatives[174),175] have been reported. The formation of 3-phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo[2.2.0]hex-5-ene (195) is enhanced in aprotic solvents such as benzene, dioxane, and acetone. However, acetonitrile showed no influence compared with a protic solvent such as methanol upon the photo-reaction. (Table 31)

Table 31 The Photochemical Reaction of 32 in Various Solvents Under an Argon for 15 hr

| Solvent | Additive | Yield[a] (32,%) |
|---|---|---|
| Benzene | | 72 |
| Benzene | Benzophenone | 15 |
| Benzene | Acetophenone | 15 |
| Benzene | Penta-1,3-diene | 51 |
| Dioxane | | 50 |
| Acetonitrile | | 15.5 |
| Propan-2-ol | | 33.5 |
| Methanol | | 15 |
| Water | | Trace |

a) Determined by GLC.

The quantum yields for the photochemical electrocyclization of (32) and (4) [to (195) and (199)] were 0.52 and 0.79 in

benzene, and that of (32) was 0.04 in methanol. (Table 30) The photo-reaction of 32 was quenched slightly by pentan-1,3-diene, and was not affected by triplet sensitizers such as benzophenone and acetophenone. (Table 31) The above results indicate that the photochemical electrocyclization of 32 to 195 proceeds mainly via the singlet state, considering that this photo-reaction is an intramolecular one.

It is concluded that by irradiation of 1,4,6-trisubstituted 2(1H)-pyrimidinones in benzene with high-pressure mercury lamp, the photochemical electrocyclization products, 3,4,6-trisubstituted 2-oxo-1,3-diazabicyclo[2.2.0]hex-5-enes, are obtained in 14-85% yield. Although the bicyclo-[2.2.0] system is generally unstable, these photo-isomers are stable at room temperature.

## IV THE REACTIONS AND SYNTHETIC UTILITIES OF REDUCED 2(1H)-PYRIMIDINONES

For convenience, 2(1H)-pyrimidinones which have either partially or completely hydrogenated double bonds, are called " reduced " 2(1H)-pyrimidinones. There are four types of reduced 2(1H)-pyrimidinones as shown in Fig. 13.

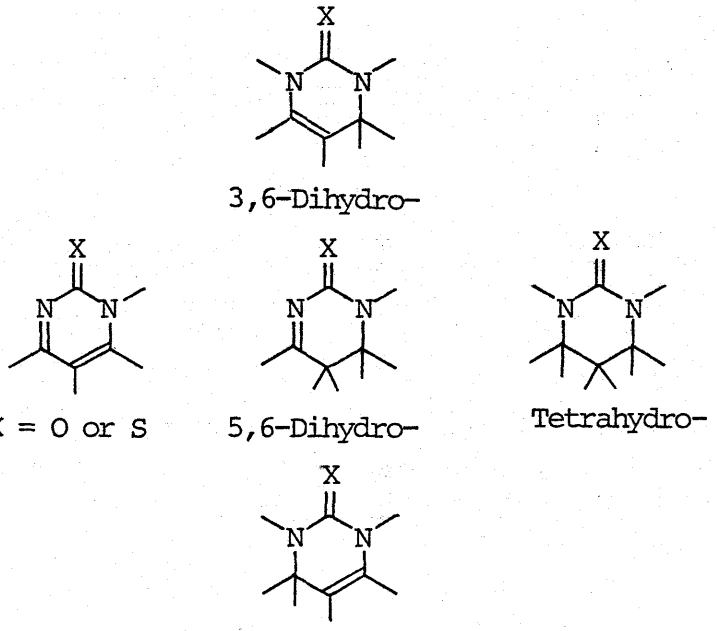


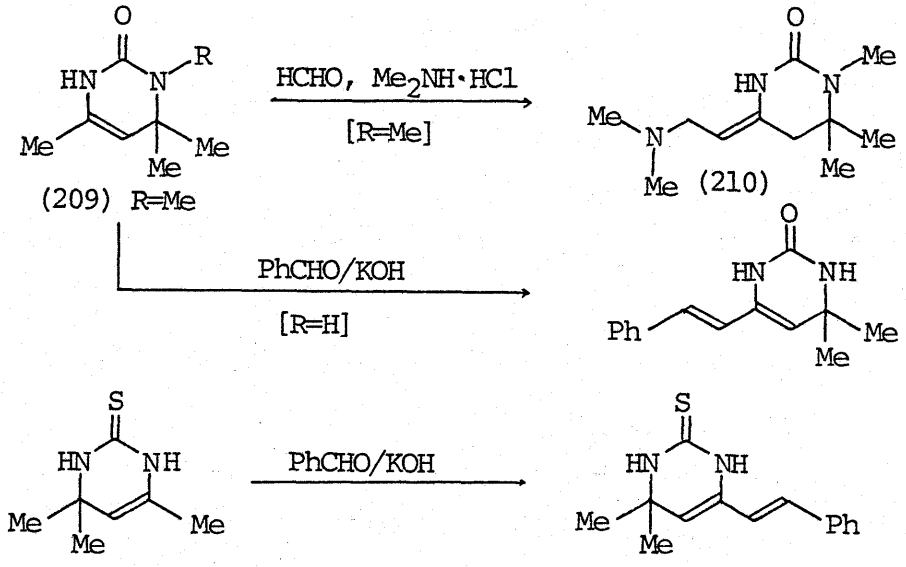

Fig. 13 Reduced 2(1H)-Pyrimidinones

However, a paper concerning the preparation of 5,6-dihydro- derivatives has not previously been reported.

Some papers on the reaction of reduced 2(1H)-pyrimidinones have been reported. 3,6-Dihydro-1,4,6,6-tetramethyl-

2(1H)-pyrimidinone (209) undergoes Mannich reaction to give the C-C bond formation product (210)[73]. The Aldol type condensation on the allylic methyl group of 1-unsubstituted 2(1H)-pyrimidinones has also been reported[83),84)].

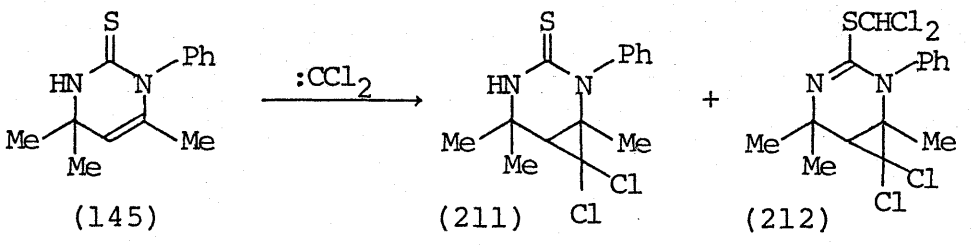
(Scheme 36)




Scheme 36

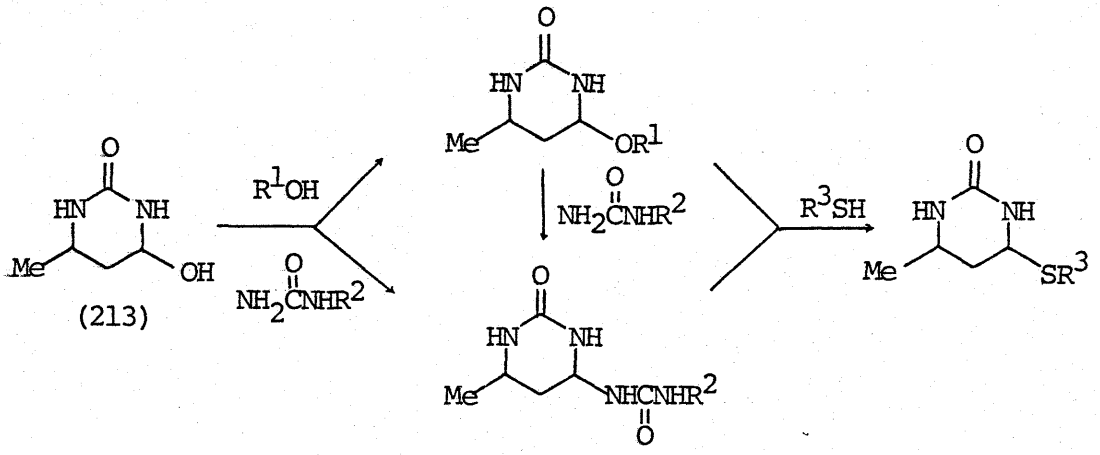
3,4-Dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinethione (145) reacts with dichlorocarben to afford the addition product (211) and the S-H insertion product (212)[176),177)].

(Scheme 37)



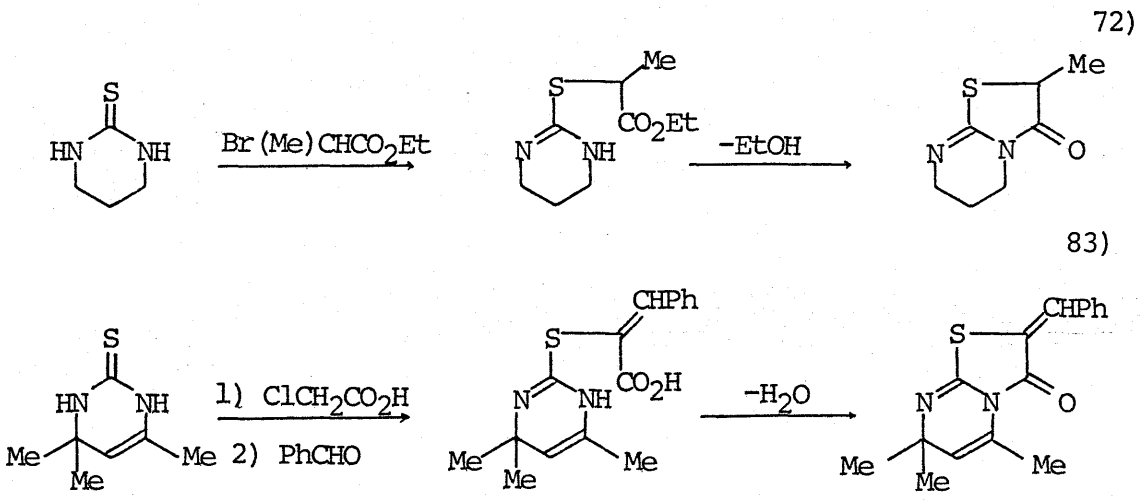

Scheme 37

4-Methyl-6-hydroxy-tetrahydro-2(1H)-pyrimidinone (213) undergoes nucleophilic substitution at C-6 position with various alcohols, thiols, and ureas to yield a variety of 6-substituted tetrahydro-2(1H)-pyrimidinones[178)-183)]. (Scheme 38)



Scheme 38

The ring formation reaction using 1-unsubstituted tetrahydro-2(1H)-pyrimidinethiones has been reported. (Scheme 39)

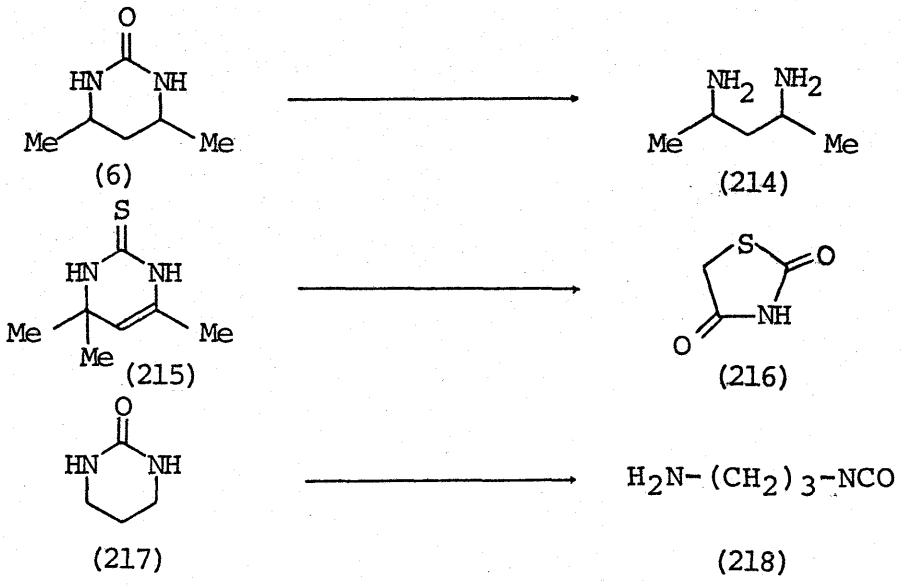


72)

83)

Scheme 39

Also a few papers concerning the synthetic utilities of reduced 2(1H)-pyrimidinones have been reported. Tetrahydro-4,6-dimethyl-2(1H)-pyrimidinone (6), for example, is hydrolyzed with 60% sulfuric acid to give 2,4-diaminopentane (214)[11]. 3,4-Dihydro-4,4,6-trimethyl-2(1H)-pyrimidinethione (215) is converted into thiazolidine-2,4-dione (216) by the action of chloroacetic acid[184]. By the thermolysis of tetrahydro-2(1H)-pyrimidinone (217), γ-aminoisocyanate (218) is obtained[185]. (Scheme 40)

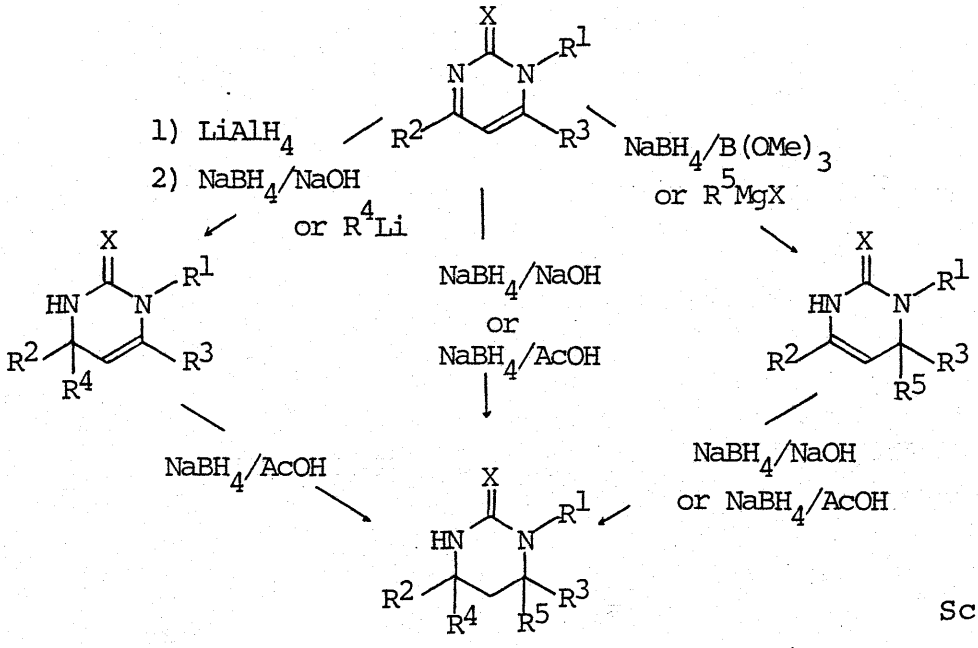



Scheme 40

As mentioned above, the chemistry of reduced 2(1H)-pyrimidinones, especially 1-substituted derivatives, has largely unexplored.

In the previous section (III-3), the author established the regioselective preparation of three types of reduced

2(1H)-pyrimidinones by the reaction of 2(1H)-pyrimidinones with organometallic reagents or metal hydride complexes under various conditions[155),159)]. (Scheme 41)




Scheme 41

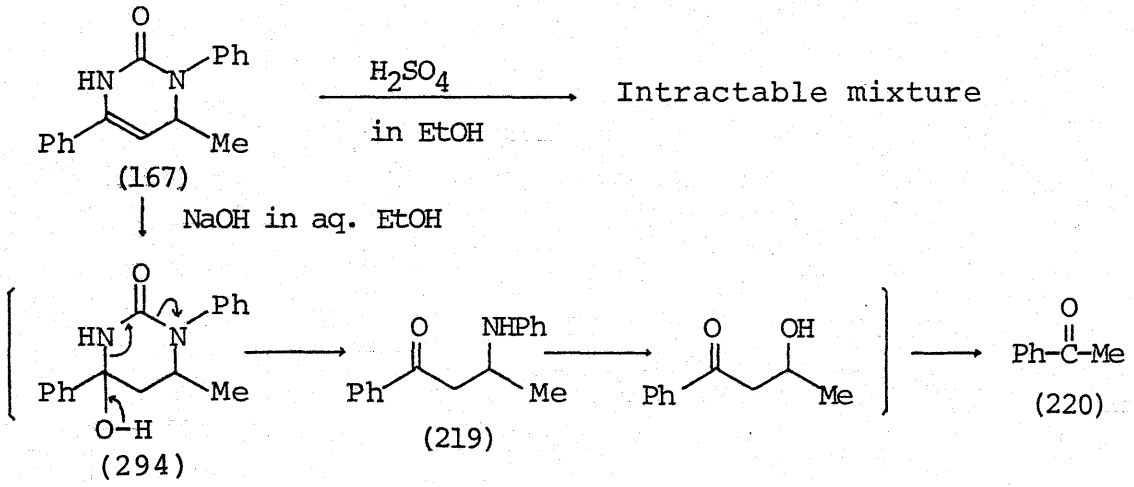
X = O or S; $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ = H, Alkyl, Aryl

Since reduced 2(1H)-pyrimidinones have either partially or completely hydrogenated double bonds, they should lose the aromaticity of the pyrimidine ring. So, reduced 2(1H)-pyrimidinones can be expected to exhibit the properties of enamines and cyclic ureas.

Therefore, the author investigated the reactions and synthetic utilities of reduced 2(1H)-pyrimidinones.

## IV-1 The Ring Opening Reaction with Hydroxylamine[186)]

3,6-Dihydro-6-methyl-1,4-diphenyl-2(1H)-pyrimidinone (167) was treated with sulfuric acid in ethanol, but any products could not be obtained. On the other hand, treating of the compound 167 with sodium hydroxide in aqueous ethanol, acetophenone (220) was obtained. The possible mechanism for the decomposition of 167 is speculated as follows. (Scheme 42)




Scheme 42

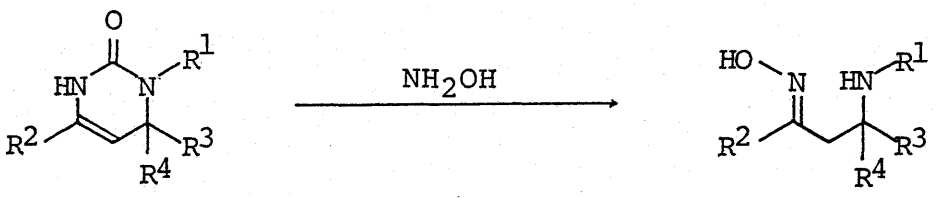
Hydroxyl anion attacks C-4 carbon and then the adduct 294 undergoes the ring opening reaction to form the intermediate (219). By substitution of aniline by hydroxyl anion and subsequent retro-Aldol reaction, acetophenone (220) is formed. For the purpose of the trapping of the intermediate 219, the reaction of 3,6-dihydro-2(1H)-pyrimidinones with hydroxylamine was attempted.

When 3,6-dihydro-4,6,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (137) reacted with hydroxylamine hydrochloride in the presence of sodium hydroxide in absolute ethanol, the product, bp 100 °C/$10^{-4}$ mmHg, the formula $C_{12}H_{17}N_2O$, and a broad band at 2800-3500 $cm^{-1}$ due to O-H stretching in the IR spectrum, was obtained. The PMR spectrum showed at δ 1.33 (s, 6H), 1.90 (s, 3H), and 2.54 ppm (s, 2H) attributable to geminal dimethyl, methyl, and methylene protons, respectively, in addition to the characteristic peaks of the aniline protons at δ 6.6-7.0 (m, 3H) and 7.0-7.4 ppm (m, 2H). The product was found to be 2-anilino-2-methyl-pentan-4-one oxime (221) by these spectral data and comparison with a sample independently prepared from mesityl oxide, aniline, and hydroxylamine. The reaction of other 1,4,6-trisubstituted 3,6-dihydro-2(1H)-pyrimidinones with hydroxylamine was examined, and the results were summarized in Table 32.

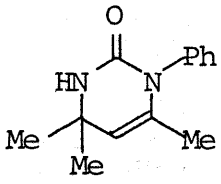
3,4-Dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (138) and dihydro-2(1H)-pyrimidinethiones (164 and 165) did not react with hydroxylamine under the same condition. (Table 32)

When 3,6-dihydro-6-methyl-1-phenyl-2(1H)-pyrimidinone (153) was also treated with hydroxylamine, two products, bp 120 °C/$10^{-4}$ mmHg (compound A) and mp 55-57 °C (compound B), were formed. Compound A was assigned to be 2-anilinobutan-4-one oxime (226) by means of the spectral data and elemental analysis. Compound B showed two strong IR bands at 3360 and

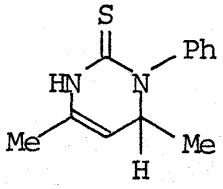
Table 32 The Reaction with Hydroxylamine



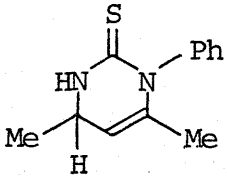

| Compd No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Product No | Bp(°C) ($/10^{-4}$mmHg) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 137 | Ph | Me | Me | Me | 221 | 100 | 68 |
| 159 | Ph | Me | Me | H | 222 | 90 | 72 |
| 223 | p-$ClC_6H_4$ | Me | Me | H | 224 | 123 | 78 |
| 167 | Ph | Ph | Me | H | 225 | 140 | 63 |
| 153 | Ph | H | H | Me | 226 | 120 | 10 |




(138)

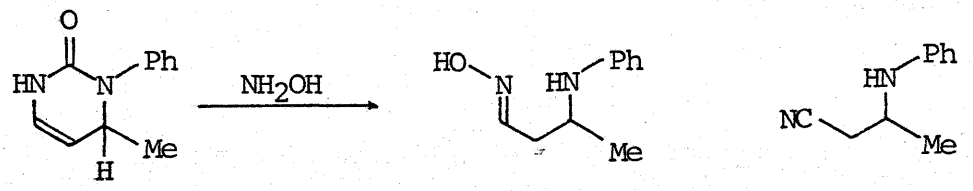



(164)




(165)

2250 $cm^{-1}$ due to the N-H and C≡N stretching, respectively. The PMR spectrum showed at δ 1.32 (d, 3H, J=6.0 Hz) and 2.48 ppm (t, 2H, J=4.0 Hz) assignable to methyl and methylene protons as well as the chracteristic peaks of the aniline protons at δ 6.5-6.9 (m, 3H) and 7.0-7.4 ppm (m, 2H). From these data, compound B was deduced to be 2-anilino-butyronitrile (227), which was identical an authentic sample (mp 57-58 °C) obtained from crotononitrile and aniline[187].



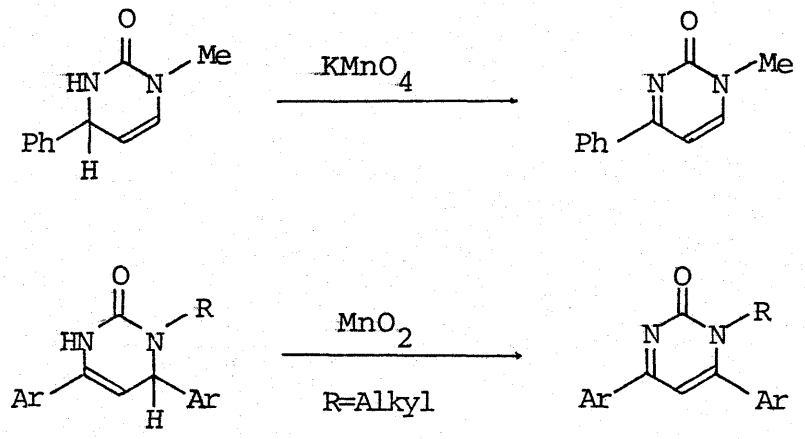

(153) (226) (227)

Yield 10% 23%

It is concluded that 1,4,6-trisubstituted 3,6-dihydro-2(1H)-pyrimidinones undergo the ring opening reaction with hydroxylamine to afford oximes and nitrile in good yields.

## IV-2 Facile Oxidation with Chloranil[188)]

There have been many reports on the preparation of 2(1H)-pyrimidinones. (See INTRODUCTION) However, only two attempts to prepare 2(1H)-pyrimidinones by the oxidation of dihydro-2(1H)-pyrimidinones with potassium permanganate[91)] or manganese dioxide[42),93)] have been carried out by Hardtmann. (Scheme 43)

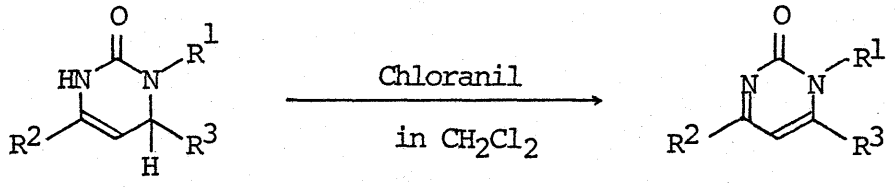



Scheme 43

In this section, the author investigated the oxidation of 1-aryl-dihydro-2(1H)-pyrimidinones.

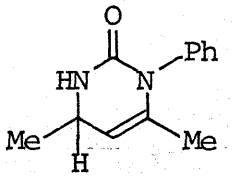
3,6-Dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (159) was treated with manganese dioxide or potassium ferricyanide to recover the starting material. Further, the author tried the oxidation of the compound 159 with potassium permanganate or potassium permanganate in the presence of phase transfer catalysis, $PhCH_2\overset{+}{N}Et_3 \cdot Cl^-$, to give an intract-

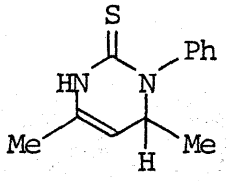
Table 33 The Oxidation with Chloranil

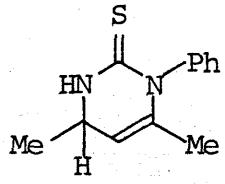



| Compd. No | $R^1$ | $R^2$ | $R^3$ | Product No | Yield[a] (%) |
|---|---|---|---|---|---|
| 159 | Ph | Me | Me | 32 | 96 |
| 228 | p-$MeC_6H_4$ | Me | Me | 33 | 94 |
| 229 | m-$MeC_6H_4$ | Me | Me | 38 | 96 |
| 230 | m-$MeOC_6H_4$ | Me | Me | 39 | 98 |
| 167 | Ph | Ph | Me | 54 | 99 |
| 169 | Ph | Me | Ph | 55 | 88 |

a) Determined by LPC.


(160)


(164)

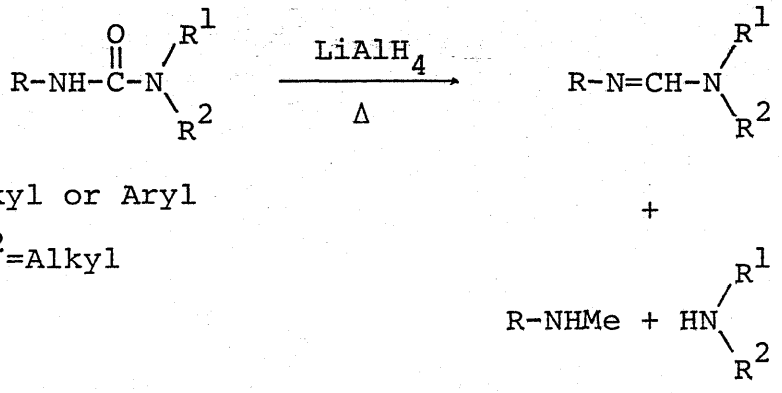

(165)

able mixture in both cases. On the contrary, the compound 159 was smoothly oxidized with 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil) in dichloromethane at room temperature to afford 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) in 96% yield. The similar oxidation of other 3,6-dihydro-2(1H)-pyrimidinones was attempted, and the results were shown in Table 33. The isomeric 3,4-dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (160) was also oxidized with chloranil to yield 2(1H)-pyrimidinone (32), but the oxidation product could not be obtained in the case of 3,6-dihydro- (164) and 3,4-dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (165). (Table 33)

In conclusion, 1-aryl-dihydro-2(1H)-pyrimidinones are easily oxidized with chloranil to afford the corresponding 2(1H)-pyrimidinones in high yields under a mild condition.

## IV-3 The Reductive Ring Opening Reaction with $LiAlH_4$[189)]

Diamines are useful compounds as synthetic intermediates and ligands of metal chelates[190),191)]. Although many papers have been reported on the synthesis of 2,4-diaminopentanes[192)-194)], the great majority of these works has been concerned with N-unsubstituted or N-alkyl substituted 2,4-diaminopentanes. Hutchins and Maryanoff reported on the preparation of 2,4-diaminopentane from tetrahydro-4,6-dimethyl-2(1H)-pyrimidinone by the hydrolysis with 60% sulfuric acid under heating at 160 °C for 4 days[11)]. In 1964, Larizza et al. reported that N,N,N'-trisubstituted ureas were reduced with lithium aluminum hydride to give a mixture of two amines under drastic conditions[195)]. (Scheme 44)



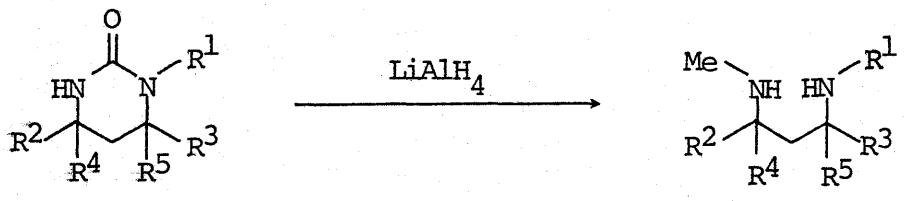

Scheme 44

Since 1-aryl-tetrahydro-2(1H)-pyrimidinones are regarded as N,N,N'-trisubstituted cyclic ureas, they seems to be important

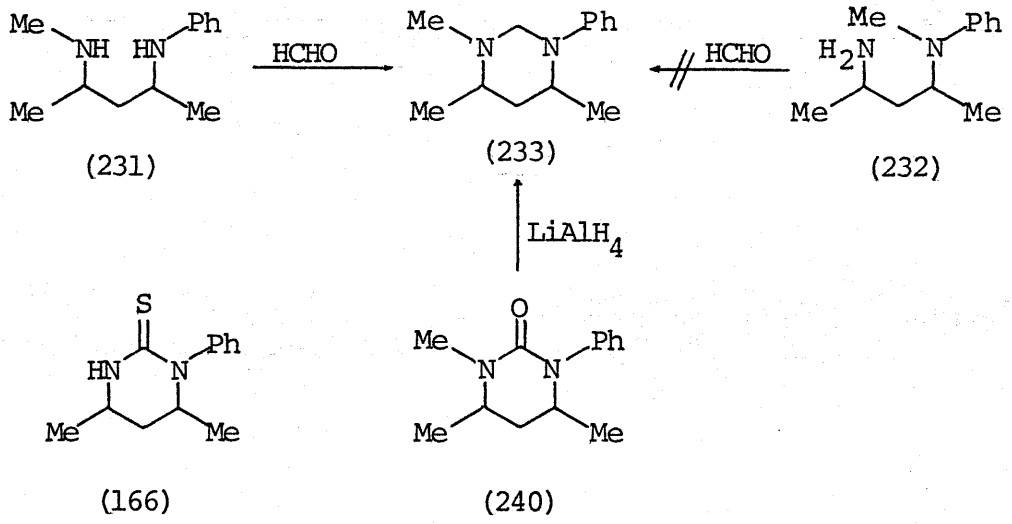
precursor for the preparation of N-aryl-2,4-diaminopentanes. Therefore, the author investigated the preparation of N-aryl-2,4-diaminopentanes by the reductive ring opening reaction with $LiAlH_4$.

When tetrahydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (161) was refluxed for 20 hr with $LiAlH_4$ in tetrahydrofuran-benzene mixture, the colorless viscous oil, bp 58 °C/ $10^{-4}$ mmHg, was obtained. The product had the formula $C_{12}H_{20}N_2$ and was found to be fairly basic. The IR absorption band at 1660 $cm^{-1}$ due to the C=O stretching in the starting material 161 disappeared, and the band at 3280 $cm^{-1}$ attributable to the N-H stretching was observed. The PMR spectrum showed signals at δ 1.05 (d, 3H, J=6.0 Hz, $CH_3$), 1.15 (d, 3H, J=6.0 Hz, $CH_3$), and 2.34 ppm (s, 3H, N-$CH_3$). Further, the PMR spectrum exhibited the characteristic peaks of the aniline protons at δ 6.5-6.9 (m, 3H) and 7.1-7.4 ppm (m, 2H), and observed two deuterium exchangeable protons at δ 2.94 (br. s., 2H, 2N-H). From these data, two possible structures (231 and 232) were proposed. The methyl protons of dimethylamine appear at δ 2.43, while those of N,N-dimethylaniline appear at 2.92 ppm[196]. Further, compound 231 was treated with formaldehyde to yield 3,4,6-trimethyl-1-phenylhexahydropyrimidine (233). (Table 34) Thus, the structure of 232 seemed to be unlikely, and the product was assigned to be 2-anilino-4-methylaminopentane (231). The reductive ring opening reaction of similar

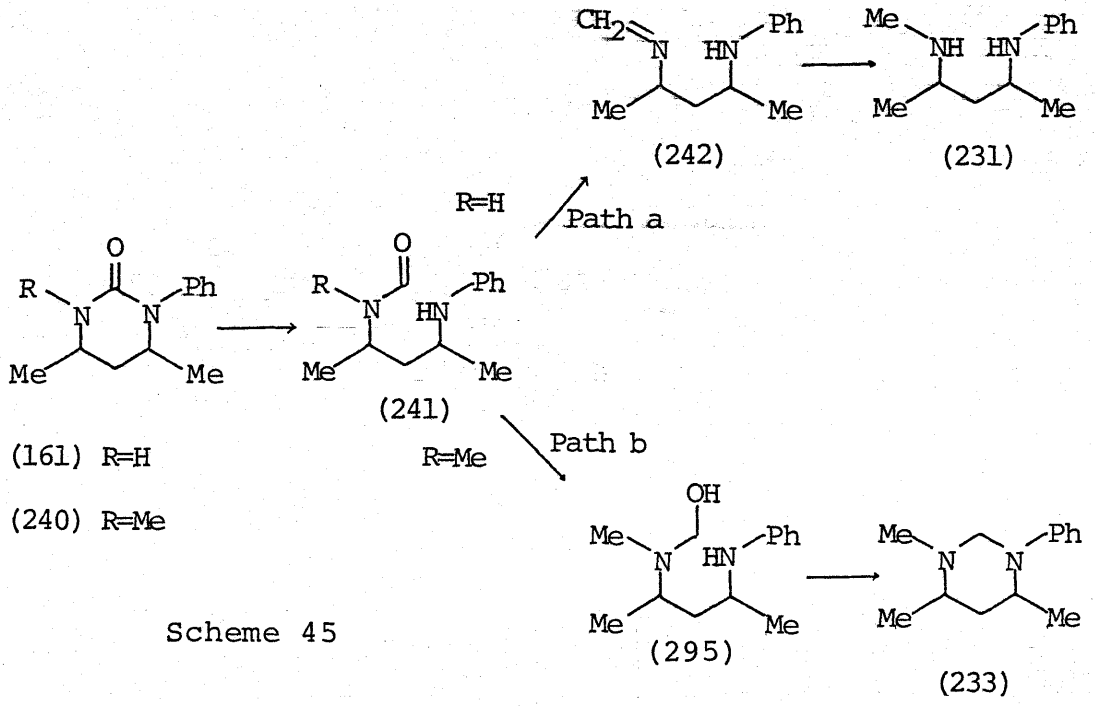
Table 34 The Preparation of N-Aryl-2,4-diaminopentanes




| Compd. No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Product No | Bp(°C) (/$10^{-4}$mmHg) | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 161 | Ph | Me | Me | H | H | 231 | 58 | 75 |
| 175 | p-$MeC_6H_4$ | Me | Me | H | H | 234 | 60 | 59 |
| 176 | p-$MeOC_6H_4$ | Me | Me | H | H | 235 | 70 | 54 |
| 236 | Ph | Me | Me | H | Me | 237 | 42 | 37 |
| 238 | Ph | Me | Me | Me | H | 239 | 63 | 40 |



tetrahydro-2(1H)-pyrimidinones with $LiAlH_4$ was examined, and the results were listed in Table 34. Also, the reduction of tetrahydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (166) was carried out in the manner described above, but the starting material 166 was recovered. Finally, the author examined the reduction of tetrahydro-3,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (240), which was regarded as tetrasubstituted urea, to give only hexahydropyrimidine (233) in 60% yield. (Table 34) The possible reaction mechanism for the reduction with $LiAlH_4$ is speculated as follows. (Scheme 45)




Scheme 45

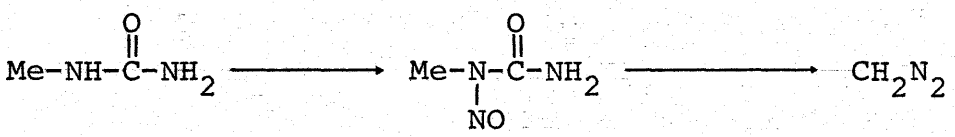
First, the reductive ring opening reaction occurs to form N-formyl diamine (241). In the case of 161 (R=H), 2-anilino-

4-methylaminopentane (231) is obtained by reduction of the resulting imine (242). (Path a) On the other hand, in the case of 240 (R=Me), the formyl group of 241 is reduced with $LiAlH_4$ and the resulting 295 cyclizes to afford 3,4,6-trimethyl-1-phenylhexahydropyrimidine (233). (Path b)

In conclusion, the preparation of N-aryl-2,4-diaminopentanes is accomplished by the reductive ring opening reaction of 1-aryl-tetrahydro-2(1H)-pyrimidinones on treating with $LiAlH_4$. Further, it is found that tetrahydro-3,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone give a cyclic diamine which is reduced only carbonyl group.

## IV-4 The N-Nitrosation and Decomposition[197]

Many papers on the preparation of various N-nitrosoamines have been reported in relation to their powerful chemical carcinogens[198),199)]. On the contrary, the attempt to prepare nitroso-2(1H)-pyrimidinones has not been reported. Whereas it is well known that N-methylurea reacts with sodium nitrite to give N-nitrosomethylurea[200)], which is decomposed with aqueous potassium hydroxide to yield diazomethane[201)]. (Scheme 46)

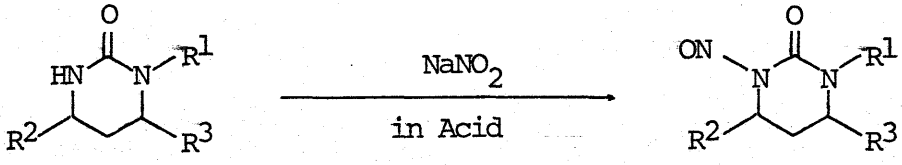


Scheme 46

Since tetrahydro-2(1H)-pyrimidinones are considered to be cyclic ureas, it is possible to undergo the nitrosation on nitrogen at N-3 position in the pyrimidine ring. Therefore, the author investigated the preparation and decomposition of 3-nitroso-tetrahydro-2(1H)-pyrimidinones.

When tetrahydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (161) was treated with sodium nitrite in 6N hydrochloric acid, the product, mp 114-115 °C, was obtained. The product had the formula $C_{12}H_{15}N_3O_2$. The IR absorption

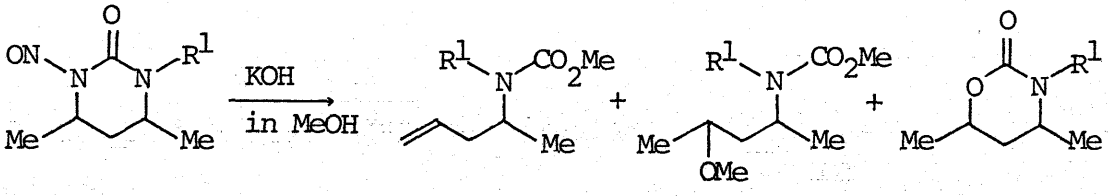
Table 35 The Nitrosation of Tetrahydro-2(1H)-pyrimidinones




| Compd. No | $R^1$ | $R^2$ | $R^3$ | Acid[a] | Product No | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 161 | Ph | Me | Me | A | 243 | 114-115 | 93 |
| 174 | Me | Ph | Ph | A | 244 | 175-176[b] | 42 |
| 175 | p-$MeC_6H_4$ | Me | Me | A | 245 | 198-200[b] | 70 |
| 176 | p-$MeOC_6H_4$ | Me | Me | A | 246 | 87-88 | 87 |
| 177 | p-$ClC_6H_4$ | Me | Me | B | 247 | 108-110 | 68 |
| 248 | p-$BrC_6H_4$ | Me | Me | B | 249 | 116-117 | 48 |
| 250 | p-$MeC_6H_4$ | H | H | A | 251 | 160-161[b] | 92 |
| 252 | Ph | H | Me | A | 253 | 93-94 | 96 |

a) A=6N Hydrochloric acid. B=Concentrated hydrochloric acid.
b) Decomposition.

Table 36 The Decomposition of 3-Nitroso-2(1H)-pyrimidinones




(243) $R^1$=Ph (254) 40% (255) 29% (256) 17%

(245) $R^1$=p-$MeC_6H_4$ (257) 40% (258) 21% (259) 20%

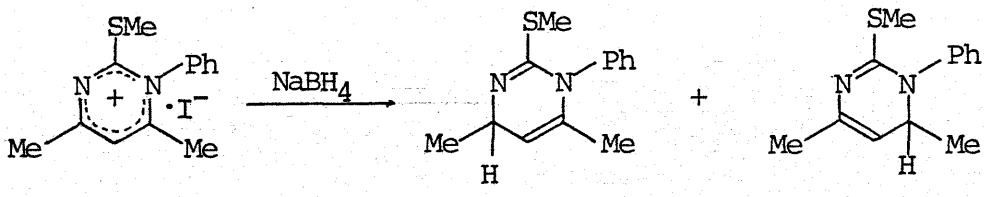
band at 1690 $cm^{-1}$ due to the C=O stretching was observed, but the band at 3200 $cm^{-1}$ attributable to the N-H stretching of the starting material 161 disappeared. The PMR spectrum showed two methyl signals at δ 1.08 (d, 3H, J=7.0 Hz) and 1.25 ppm (d, 3H, J=7.0 Hz). From these data, the product was determined to be tetrahydro-4,6-dimethyl-3-nitroso-2(1H)-pyrimidinone (243). Similarly, the nitrosation of other tetrahydro-2(1H)-pyrimidinones was tried, and the results were listed in Table 35.

The decomposition of the resulting tetrahydro-3-nitroso-2(1H)-pyrimidinones was attempted. The compounds 243 and 245 were treated with potassium hydroxide in methanol to give methyl N-substituted N-arylcarbamates (254, 255, 257, and 258) and 4,6-dimethyl-3-aryl-tetrahydro-1,3-oxazin-2-ones (256 and 259). (Table 36) The structure of these products was determined by means of the spectral data and elemental analyses.

In conclusion, tetrahydro-2(1H)-pyrimidinones react with sodium nitrite to give the corresponding 3-nitroso-2(1H)-pyrimidinones in good yields. However, the selective decomposition of them is unsuccessful, because the decomposition of 3-nitroso-2(1H)-pyrimidinones affords two kinds of methyl N-substituted N-arylcarbamates and tetrahydro-1,3-oxazin-2-ones.

## IV-5 The S-Methylation with Methyl Iodide

4,6-Dimethyl-2-methylthio-1-phenylpyrimidinium iodide (91) was reduced with $NaBH_4$ to afford a mixture of 1,4-dihydro- (260) and 1,6-dihydro-4,6-dimethyl-2-methylthio-1-phenylpyrimidine (261) which could not separate unfortunately[7]. (Scheme 47)



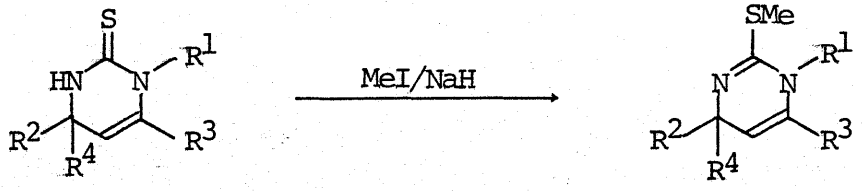

(91) (260) (261)

Scheme 47

It is well known that thiourea react with alkyl halides to give the S-alkylated products in high yields[202]. Since dihydro-2(1H)-pyrimidinethiones were considered to be cyclic thioureas, the author investigated the S-methylation with methyl iodide.

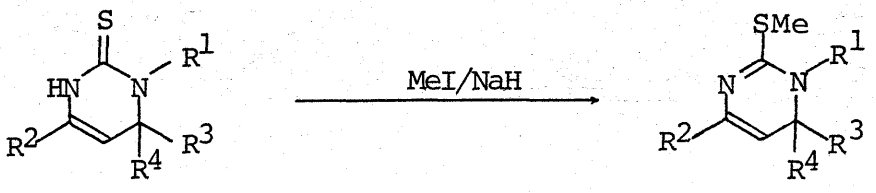
3,4-Dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinethione (145) was treated with methyl iodide in the presence of sodium hydride to give the product, mp 44-45 °C, which had the formula $C_{14}H_{18}N_2S$. The IR absorption band at 3180 $cm^{-1}$ due to the N-H stretching of the starting material 145 disappeared. The PMR spectrum exhibited signals at δ 1.26 (s, 6H) and 1.44 ppm (d, 3H, J=1.2 Hz) attributed to the allyl coupling of C-6 methyl protons with C-5 olefinic

Table 37 The S-Methylation of 3,4-Dihydro-2(1H)-Pyrimidinethiones




| Compd. No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Product No | Yield (%) |
|---|---|---|---|---|---|---|
| 165 | Ph | H | Me | Me | 260 | 87 |
| 145 | Ph | Me | Me | Me | 262 | 88 |
| 170 | Ph | H | Ph | Me | 263 | 74 |
| 264 | p-$MeC_6H_4$ | Me | Me | Me | 265 | 98 |
| 266 | p-$MeOC_6H_4$ | Me | Me | Me | 267 | 94 |

Table 38 The S-Methylation of 3,6-Dihydro-2(1H)-Pyrimidinethiones




| Compd. No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Product No | Yield (%) |
|---|---|---|---|---|---|---|
| 164 | Ph | Me | H | Me | 261 | 93 |
| 144 | Ph | Me | Me | Me | 268 | 87 |
| 269 | p-$MeC_6H_4$ | Me | H | Me | 270 | 86 |

proton. Further, it showed a new signal at δ 2.33 ppm (s, 3H) assignable to S-methyl protons. From these data, the product was determined to be 1,4-dihydro-4,4,6-trimethyl-2-methylthio-1-phenylpyrimidine (262). When 3,6-dihydro-4,6,6-trimethyl-1-phenyl-2(1H)-pyrimidinethione (144) was treated with methyl iodide under the same condition, the product, mp 72-74 °C, was obtained. The product was deduced to be 1,6-dihydro-4,6,6-trimethyl-2-methylthio-1-phenyl-pyrimidine (268), which was structurally isomeric with 262. The structure of the compounds 262 and 268 was also supported by UV spectral evidence. Eisner reported that 1,4-dihydro-1-trimethylsilylpyridine exhibited the absorption band at 288 nm, and 1,2-dihydro-1-trimethylsilylpyridine exhibited at 320 nm[203]. The absorption band of 1,4-dihydropyrimidine (262) displayed at 238 nm (logε= 3.78), while that of 1,6-dihydropyrimidine (268) displayed at 286 nm (logε= 3.69). The S-methylation of other dihydro-2(1H)-pyrimidinethiones was carried out, and the results were summarized in Table 37 and 38.

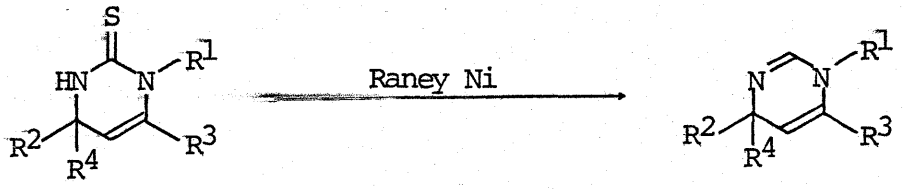
It is concluded that 3,4- and 3,6-dihydro-2(1H)-pyrimidinethiones are treated with methyl iodide in the presence of sodium hydride to give 2-methylthio-1,4- and 1,6-dihydropyrimidines in high yields.

## IV-6 The Desulfuration with Raney Nickel

The synthesis and reaction of 1,4-dihydropyridines and their derivatives have been extensively studied as model compounds of NAD(P)H[203]. However, dihydropyrimidines have scarecely investigated in spite of aza-analogues of dihydropyridines[204),205)]. In the previous section (III-4), the author reported that 2(1H)-pyrimidinethiones were desulfurized with Raney nickel to give 1,2-dihydropyrimidines. As an extensive study of desulfuration, the author investigated the desulfuration of dihydro-2(1H)-pyrimidinethiones with Raney nickel.

3,4-Dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinethione (145) was warmed with Raney nickel in methanol at 50 °C for 1 hr, then refluxed for another 2 hr to afford the product which had the formula $C_{13}H_{16}N_2$. The IR absorption band at 3180 $cm^{-1}$ due to the N-H stretching of the starting material 145 disappeared. The PMR spectrum exhibited signals at δ 1.25(s, 6H), 1.55 (d, 3H, J=1.3 Hz), and 4.47 ppm (q, 1H, J=1.3 Hz) attributable to C-4 geminal dimethyl, C-6 methyl, and olefinic protons, respectively. The CMR spectrum showed a new doublet at δ 144.38 ppm assignable to C-2 $sp^2$-carbon of the pyrimidine ring. From these data, the product was determined to be 1,4-dihydro-4,4,6-trimethyl-1-phenylpyrimidine (273). Similarly, the treatment of other 3,4-dihydro-2(1H)-pyrimidinethiones with Raney nickel

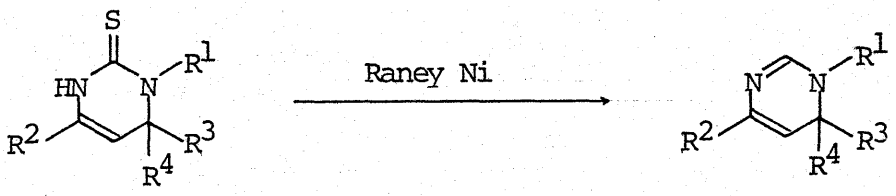
Table 39 The Desulfuration of 3,4-Dihydro-2(1H)-Pyrimidinethiones




| Compd. No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Product No | Yield (%) |
|---|---|---|---|---|---|---|
| 145 | Ph | Me | Me | Me | 271 | 81 |
| 165 | Ph | H | Me | Me | 272 | 50 |
| 264 | p-$MeC_6H_4$ | H | Me | Me | 273 | 63 |
| 266 | p-$MeOC_6H_4$ | H | Me | Me | 274 | 74 |
| 275 | p-$MeC_6H_4$ | Me | Me | Me | 281 | 82 |
| 276 | p-$MeOC_6H_4$ | Me | Me | Me | 282 | 72 |
| 277 | p-$ClC_6H_4$ | Me | Me | Me | 283 | 81 |
| 278 | p-$BrC_6H_4$ | Me | Me | Me | 284 | 55 |
| 279 | m-$MeC_6H_4$ | Me | Me | Me | 285 | 98 |
| 280 | $PhCH_2$ | Me | Me | Me | 286 | 83 |

gave 1,4-dihydropyrimidines. (Table 39) When 3,6-dihydro-1-methyl-4,6-diphenyl-2(1H)-pyrimidinethione (287) was treated with Raney nickel in the similar manner, 1,6-dihydro-1-methyl-4,6-diphenylpyrimidine (288) was obtained in 35% yield. The structure of the product 288 was determined by comparison of the spectral data with those of reported by van der Plas et al.[206]. The desulfuration of other 3,6-dihydro-2(1H)-pyrimidinethiones was attempted, and the results were listed in Table 40.

Table 40 The Desulfuration of 3,6-Dihydro-2(1H)-Pyrimidinethiones




| Compd. No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Product No | Yield (%) |
|---|---|---|---|---|---|---|
| 164 | Ph | Me | H | Me | 289 | 20 |
| 269 | p-$MeC_6H_4$ | Me | H | Me | 290 | 49 |
| 291 | p-$MeOC_6H_4$ | Me | H | Me | 292 | 31 |

From the results of section (III-4) and this section, it is concluded that the selective preparation of three types of dihydropyrimidines is accomplished by the desulfuration of 2(1H)-pyrimidinethiones or dihydro-2(1H)-pyrimidinethiones with Raney nickel.

4-(p-Methoxy)phenyl-6-methyl-1-phenyl-2(1H)-pyrimidinone (57)

(from ethyl acetate-hexane); IR: 1635, 1010, 820, 780, 760, and 690; PMR: 2.03 (d, 3H, J=0.7 Hz), 3.87 (s, 3H), 6.73 (q, 1H, J=0.7 Hz), 6.9-7.6 (m, 7H), and 8.1-8.3 (m, 2H).

4-(p-Chloro)phenyl-6-methyl-1-phenyl-2(1H)-pyrimidinone (58)

(from benzene-hexane); IR: 1640; PMR: 2.07 (d, 3H, J=0.7 Hz), 6.72 (q, 1H, J=0.7 Hz), 7.2-7.6 (m, 7H), and 8.0-8.3 (m, 2H).

4-Methyl-1,6-diphenyl-2(1H)-pyrimidinethione (59)

(from ethanol); IR: 3010, 1260, 760, and 740; PMR: 2.49 (s, 3H), 6.60 (s, 1H), and 7.1-7.4 (m, 10H).

4-Methyl-1-phenyl-6-(p-tolyl)-2(1H)-pyrimidinethione (60)

(from benzene-hexane); IR: 3020, 1260, 800, 760, and 690; PMR: 2.07 (s, 3H), 2.50 (s, 3H), 6.58 (s, 1H), 7.0-7.4 (m, 9H).

6-(p-Methoxy)phenyl-4-methyl-1-phenyl-2(1H)-pyrimidine-thione (61)

(from benzene-hexane); IR: 3020, 1500, 1240, 1025, 820, and 695; PMR: 2.50 (s, 3H), 3.72 (s, 3H), 6.60 (s, 1H), 6.7-7.5 (m, 9H).

6-(p-Chloro)phenyl-4-methyl-1-phenyl-2(1H)-pyrimidine-thione (62)

(from benzene-hexane); IR: 1265; PMR: 2.52 (s, 3H), 6.55 (s, 1H), and 6.8-7.3 (m, 9H).

Method B The solution of acetylacetone (0.41 mol) and

# V EXPERIMENTAL

Melting points and boiling points were uncorrected. IR spectra were taken in KBr pellets in the case of solid samples and by the film method in the case of liquid samples, using a Jasco ITA-1 Infrared Spectrophotometer. IR frequences are reported in wave numbers ($cm^{-1}$). PMR and CMR spectra were determined with Hitachi R-20 and JEOL-100 spectrometer, respectively, using tetramethylsilane as an internal standard. The chemical shifts are in δ-units (ppm) with coupling constants in Hz, and $CDCl_3$ was used as a solvent unless otherwise stated. UV spectra were measured on a Shimadzu UV-365 UV-VIS-NIR recording spectrophotometer. Absorption maxima are reported as wavelengths (nm) followed by the logarithm of molar extinction coefficient (logε) in parentheses. MS was determined on a Hitachi RMU-6MG spectrometer. GLC was run on a Hitachi 163 Gas Chromatograph using SE-30 column. LPC was run on a Jasco Familic-100 High Pressure Micro Liquid Chromatograph on 8 cm SS-05 column with dichloromethane containing 3% methanol. The optical rotations were measured on a Union OR-50 Desital Polarimeter. Absolute rotations were determined from the PMR in the presence of the chiral shift reagent [$Eu(tfc)_3$] in $CDCl_3$ containing dichloromethane as an internal standard. A Ushio 450-W high-pressure mercury lamp was used as an irradiation source. The Force-field and INDO calculation were carried

out with a TOSBAC-5600 Type computer. For column chromatography, silica gel (Merck, Kieselgel 60, 230-400 mesh) was used. Elemental analyses were performed by Perkin-Elmer Model 240 elemental analyser.

## Preparation of 1-Aryl-2(1H)-pyrimidinones

Method A To the solution of β-diketone (40 mmol) and urea (34 mmol) in 95% ethanol (50 ml) was added concentrated hydrochloric acid (8.5 ml). The mixture was refluxed with stirring for 3 hr. The reaction mixture was then neutralized with aqueous sodium hydroxide and extracted with dichloromethane.

4,6-Dimethyl-1-(m-tolyl)-2(1H)-pyrimidinone (38)
(from benzene-hexane); IR: 1600; PMR: 1.98 (d, 3H, J=0.7 Hz), 2.30 (s, 6H), 6.12 (q, 1H, J=0.7 Hz), and 6.9-7.4 (m, 4H).

1-(m-Methoxy)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (39)
(from benzene); IR: 1655; PMR: 1.95 (d, 3H, J=0.7 Hz), 2.34 (s, 3H), 3.73 (s, 3H), 6.15 (q, 1H, J=0.7 Hz), and 6.6-7.4 (m, 4H).

4,6-Dimethyl-1-(o-tolyl)-2(1H)-pyrimidinethione (48)
(from ethanol); PMR: 1.92 (d, 3H, J=0.7 Hz), 2.10 (s, 3H), 2.40 (s, 3H), 6.56 (q, 1H, J=0.7 Hz), and 7.1-7.4 (m, 4H).

1-(o-Methoxy)phenyl-4,6-dimethyl-2(1H)-pyrimidinethione (49)
(from ethyl acetate); PMR: 2.00 (d, 3H, J=0.7 Hz), 2.40 (s, 3H), 3.73 (s, 3H), 6.62 (q, 1H, J=0.7 Hz), and 7.1-7.4 (m, 4H).

1-(o-Ethyl)phenyl-4,6-dimethyl-2(1H)-pyrimidinethione (50)

(from ethyl acetate); PMR: 1.19 (t, 3H, J=7.0 Hz), 1.94 (d, 3H, J=0.7 Hz), 2.40 (s, 3H), 2.42 (q, 2H, J=7.0 Hz), 6.62 (q, 1H, J=0.7 Hz), and 7.1-7.5 (m, 4H).

1-(o-Ethoxy)phenyl-4,6-dimethyl-2(1H)-pyrimidinethione (51)

(from ethyl acetate); PMR: 1.27 (t, 3H, J=7.0 Hz), 2.0 (d, 3H, J=0.7 Hz), 2.41 (s, 3H), 4.05 (q, 2H, J=7.0 Hz), 6.50 (q, 1H, J=0.7 Hz), and 7.1-7.4 (m, 4H).

1-(o-Chloro)phenyl-4,6-dimethyl-2(1H)-pyrimidinethione (52)

(from ethanol); PMR: 1.98 (d, 3H, J=0.7 Hz), 2.40 (s, 3H), 6.55 (q, 1H, J=0.7 Hz), and 7.2-7.6 (m, 4H).

1-(2-Methyl-3-chloro)phenyl-4,6-dimethyl-2(1H)-pyrimidinethione (53)

(from ethanol); PMR: 1.95 (d, 3H, J=0.7 Hz), 2.10 (s, 3H), 2.40 (s, 3H), 6.58 (q, 1H, J=0.7 Hz), and 7.1-7.4 (m, 3H).

6-Methyl-1,4-diphenyl-2(1H)-pyrimidinone (54)

(from benzene-hexane); IR: 3030, 1630, 770, and 760; PMR: 2.08 (d, 3H, J=0.7 Hz), 6.72 (q, 1H, J=0.7 Hz), 7.1-7.6 (m, 8H), and 7.9-8.3 (m, 2H).

4-Methyl-1,6-diphenyl-2(1H)-pyrimidinone (55)

(from ethanol-hexane); IR: 3030, 1660, 765, and 750; PMR: 2.40 (s, 3H), 6.20 (s, 1H), and 6.9-7.1 (m, 10H).

6-Methyl-1-phenyl-4-(p-tolyl)-2(1H)-pyrimidinone (56)

(from benzene-hexane); IR: 1640, 1340, 780, and 760; PMR: 2.07 (d, 3H, J=0.7 Hz), 2.40 (s, 3H), 6.80 (q, 1H, J=0.7 Hz), 7.2-7.7 (m, 7H), and 8.0-8.2 (m, 2H).

urea (0.12 mol) in distilled benzene (100 ml) was heated to reflux. After reflux, concentrated sulfuric acid (13 ml) was added dropwise to the solution cautiously. After another 5 hr refluxing, the reaction mixture was neutralized with aqueous sodium hydroxide, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. The resulting viscous oil was chromatographed on silica gel with chloroform-acetone-ethanol (100:20:4).

4,6-Dimethyl-1-(o-tolyl)-2(1H)-pyrimidinone (40)

(from benzene-hexane); IR: 1660; PMR: 2.03 (d, 3H, J=0.7 Hz), 2.48 (s, 3H), 6.28 (q, 1H, J=0.7 Hz), and 7.2-7.5 (m, 4H).

1-(o-Methoxy)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (41)

(from benzene-hexane); IR: 1660; PMR: 1.98 (d, 3H, J=0.7 Hz), 2.38 (s, 3H), 3.72 (s, 3H), 6.17 (q, 1H, J=0.7 Hz), and 6.7-7.4 (m, 4H).

1-(o-Ethyl)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (42)

(from benzene-hexane); IR: 1645; PMR: 1.18 (t, 3H, J=6.0 Hz), 1.89 (d, 3H, J=0.7 Hz), 2.40 (s,3H), 2.43 (q, 2H, J=6.0 Hz), 6.12 (q, 1H, J=0.7 Hz), and 7.0-7.4 (m, 4H).

1-(o-Ethoxy)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (43)

(from benzene-hexane); IR: 1660, 1610, 1020, 860, 800, and 760; PMR: 1.29 (t, 3H, J=7.0 Hz), 1.97 (d, 3H, J=0.7 Hz), 2.40 (s, 3H), 4.02 (q, 2H, J=7.0 Hz), 6.12 (q, 1H, J=0.7 Hz), and 6.9-7.4 (m, 4H).

1-(o-Fluoro)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (44)

(from benzene-hexane); IR: 1650, 1600, 1330, 1100, 1020, and

Table 41 Analytical Data of 1-Aryl-2(1H)-pyrimidinones

| Compd. No | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|
| 38 | $C_{13}H_{14}N_2O$ | 73.08 | 6.50 | 13.14 | 72.87 | 6.58 | 13.07 |
| 39 | $C_{13}H_{14}N_2O_2$ | 68.02 | 6.01 | 12.26 | 67.80 | 6.12 | 12.16 |
| 48 | $C_{13}H_{14}N_2S$ | 67.82 | 6.13 | 12.22 | 67.79 | 6.12 | 12.16 |
| 49 | $C_{13}H_{14}N_2OS$ | 63.37 | 5.71 | 11.59 | 63.38 | 5.72 | 11.37 |
| 50 | $C_{14}H_{16}N_2S$ | 68.86 | 6.60 | 11.44 | 68.81 | 6.60 | 11.46 |
| 51 | $C_{14}H_{16}N_2OS$ | 64.72 | 6.52 | 10.73 | 64.58 | 6.19 | 10.75 |
| 52 | $C_{12}H_{11}N_2SCl$ | 57.49 | 4.28 | 10.90 | 57.48 | 4.42 | 11.17 |
| 53 | $C_{13}H_{13}N_2SCl$ | 59.04 | 4.82 | 10.90 | 58.97 | 4.97 | 10.58 |
| 54 | $C_{17}H_{14}N_2O$ | 77.71 | 5.41 | 10.87 | 77.84 | 5.37 | 10.67 |
| 55 | $C_{17}H_{14}N_2O$ | 78.04 | 5.42 | 10.90 | 77.84 | 5.37 | 10.67 |
| 56 | $C_{18}N_{16}N_2O$ | 78.12 | 5.65 | 10.26 | 78.23 | 5.83 | 10.13 |
| 57 | $C_{18}H_{16}N_2O_2$ | 73.95 | 5.50 | 9.61 | 73.95 | 5.51 | 9.58 |
| 58 | $C_{17}H_{13}N_2OCl$ | 69.04 | 4.27 | 9.44 | 68.80 | 4.41 | 9.44 |

Table 42 Analytical Data of 1-Aryl-2(1H)-pyrimidinones

| Compd. No | Formula | Found (%) | | | Required (%) | | |
|---|---|---|---|---|---|---|---|
| | | C | H | N | C | H | N |
| 59 | $C_{17}H_{14}N_2S$ | 73.62 | 5.02 | 9.77 | 73.35 | 5.06 | 10.06 |
| 60 | $C_{18}H_{16}N_2S$ | 74.05 | 5.50 | 9.48 | 73.93 | 5.51 | 9.58 |
| 61 | $C_{18}N_{16}N_2OS$ | 70.36 | 5.16 | 8.95 | 70.10 | 5.22 | 9.08 |
| 62 | $C_{17}H_{13}N_2OCl$ | 65.53 | 4.13 | 8.76 | 65.27 | 4.18 | 8.95 |
| 40 | $C_{13}H_{14}N_2O$ | 72.61 | 6.41 | 13.11 | 72.87 | 6.58 | 13.07 |
| 41 | $C_{13}H_{14}N_2O_2$ | 67.87 | 6.13 | 12.21 | 67.81 | 6.12 | 12.71 |
| 42 | $C_{14}H_{16}N_2O$ | 73.45 | 7.02 | 12.17 | 73.65 | 7.06 | 12.27 |
| 43 | $C_{14}H_{16}N_2O_2$ | 69.04 | 6.62 | 11.69 | 68.83 | 6.60 | 11.47 |
| 44 | $C_{12}H_{11}N_2OF$ | 66.04 | 5.08 | 12.83 | 66.05 | 5.06 | 12.85 |
| 45 | $C_{12}H_{11}N_2OCl$ | 61.60 | 4.64 | 12.05 | 61.41 | 4.72 | 11.93 |
| 46 | $C_{12}H_{11}N_2OBr$ | 52.02 | 3.88 | 10.00 | 51.64 | 3.97 | 10.04 |
| 47 | $C_{16}H_{14}N_2O$ | 77.20 | 5.65 | 11.28 | 76.78 | 5.64 | 11.19 |

805; PMR: 1.98 (d, 3H, J=0.7 Hz), 2.38 (s, 3H), 6.28 (q, 1H, J=0.7 Hz), and 7.2-7.6 (m, 4H).

1-(o-Chloro)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (45)

(from benzene-hexane); IR: 1660; PMR: 2.03 (d, 3H, J=0.7 Hz), 2.48 (s, 3H), 6.28 (q, 1H, J=0.7 Hz), and 7.2-7.5 (m, 4H).

1-(o-Bromo)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (46)

(from benzene-hexane); IR: 1650, 1605, 1510, 1325, and 750; PMR: 1.95 (d, 3H, J=0.7 Hz), 2.40 (s, 3H), 6.30 (q, 1H, J=0.7 Hz), and 7.3-7.9 (m, 4H).

1-(β-Naphthyl)-4,6-dimethyl-2(1H)-pyrimidinone (47)

(from ethyl acetate-hexane); PMR: 1.97 (d, 3H, J=0.7 Hz), 2.40 (s, 3H), 6.22 (q, 1H, J=0.7 Hz), and 7.1-8.0 (m, 7H).

Reaction of β-Aminoenones with Arylisocyanates β-Aminoenone (1 mmol) was stirred for 1 hr in dry DMF (10 ml) in the presence of sodium hydride (60% in oil, 17.5 mmol) at room temperature, and then aryl—isocyanate (1 mmol) in dry DMF (5 ml) was added dropwise to the mixture in an ice-MeOH bath with stirring for 2 hr. After stirring another 1.5 hr at room temperature, the reaction mixture was poured into ice, then extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate, and evaporated off. The crude product was recrystallized from an appropriate solvent.

6-Ethyl-4-methyl-1-phenyl-2(1H)-pyrimidinone (64)

mp 159-160 °C (from benzene-hexane); IR: 1650, 1610, 1530,

790, and 700; PMR: 1.03 (t, 3H, J=8.0 Hz), 2.23 (q, 2H, J= 8.0 Hz), 6.28 (s, 1H), and 7.1-7.6 (m, 5H). Found: C 72.65, H 6.65, N 13.01. $C_{13}H_{14}N_2O$ requires C 72.87, H 6.58, N 13.07%.

1-(p-Chloro)phenyl-6-ethyl-4-methyl-2(1H)-pyrimidinone (65)

mp 146-146.5 °C (from benzene-hexane); IR: 1655, 1605, 1525, 1480, 1405, 1380, 1310, 790, and 715; PMR: 1.07 (t, 3H, J= 8.0 Hz), 2.23 (q, 2H, J=8.0 Hz), 2.40 (s, 3H), 6.23 (s, 1H), and 7.1-7.6 (m, 4H). Found: C 62.53, H 5.26, N 11.40. $C_{13}H_{13}N_2OCl$ requires C 62.78, H 5.26, N 11.26%

4-Methyl-1-phenyl-6-n-propyl-2(1H)-pyrimidinone (66)

mp 126-127.5 °C (from benzene-hexane); IR: 1650, 1520, 1325, 780, 760, and 695; PMR: 0.82 (t, 3H, J=7.0 Hz), 1.2-1.7 (m, 2H), 2.0-2.3 (m, 2H), 2.41 (s, 3H), 6.20 (s, 1H), and 7.1-7.6 (m, 5H). Found: C 73.53, H 7.07, N 12.27. $C_{14}H_{16}N_2O$ requires C 73.65, H 7.06, N 12.27%.

1-(p-Chloro)phenyl-4-methyl-6-n-propyl-2(1H)-pyrimidinone (67)

mp 205-206 °C (from benzene-hexane); IR: 1650, 1610, 1580, 1530, 1325, 780, and 715; PMR: 0.83 (t, 3H, J=7.0 Hz), 1.2-1.7 (m, 2H), 2.1-2.4 (m, 2H), 2.42 (s, 3H), 6.22 (s, 1H), and 7.1-7.6 (m, 4H). Found: C 64.32, H 5.73, N 10.61. $C_{14}H_{15}N_2OCl$ requires C 64.00, H 5.75, N 10.66%.

6-Ethyl-4-methyl-1-phenyl-2(1H)-pyrimidinethione (68)

mp 171.5-172 °C (from ethanol-hexane); IR: 1600, 1590, 1515, 1340, 1315, 1280, 1225, 755, and 690; PMR: 1.08 (t, 3H, J=8.0 Hz),

2.27 (q, 2H, J=8.0 Hz), 2.45 (s, 3H), 6.58 (s, 1H), and 7.1-7.7 (m, 5H). Found: C 67.55, H 6.08, N 12.12. $C_{13}H_{14}N_2S$ requires C 67.79, H 6.12, N 12.16%.

4-Ethyl-6-methyl-1-phenyl-2(1H)-pyrimidinethione (69)

mp 179.5-180.5 °C (from ethanol-hexane); IR: 1600, 1585, 1510, 1350, 1300, 1265, 1240, 1225, 890, 760, and 695; PMR: 1.29 (t, 3H, J=8.0 Hz), 1.98 (d, 3H, J=0.7 Hz), 2.67 (q, 2H, J=8.0 Hz), 6.61 (q, 1H, J=0.7 Hz), and 7.0-7.6 (m, 5H). Found; C 67.74, H 6.09, N 12.15. $C_{13}H_{14}N_2S$ requires C 67.79 H 6.12, N 12.16%.

1-(p-Chloro)phenyl-6-methyl-4-phenyl-2(1H)-pyrimidinone (70)

mp 249-250 °C (from benzene-hexane); IR: 1650, 1605, 1580, 1520, 1345, 815, and 765; PMR: 2.06 (d, 3H, J=0.7 Hz), 6.80 (q, 1H, J=0.7 Hz), 7.0-7.5 (m, 7H), and 8.0-8.2 (m, 2H). Found: C 68.57, H 4.36, N 9.49. $C_{17}H_{13}N_2OCl$ requires C 68.80, H 4.41, N 9.44%.

6-Methyl-1,4-diphenyl-2(1H)-pyrimidinethione (71)

mp 213.5-215 °C (decomp. from ethanol); PMR: 2.08 (d, 3H, J=0.7 Hz), 7.09 (q, 1H, J=0.7 Hz), 7.2-7.6 (m, 8H), and 8.1-8.3 (m, 2H). Found: C 73.34, H 5.05, N 10.00. $C_{17}H_{14}N_2S$ requires C 73.35, H 5.06, N 10.06%.

## Formation of Pyrimidinium Salts with D-Camphor-10-sulfonic Acid

The mixture of 1-aryl-2(1H)-pyrimidinone (8.2 mmol) with

D-camphor-10-sulfonic acid (8.2 mmol) in ethanol (20 ml) was refluxed for 1 hr with vigorous stirring. The solvent was evaporated off and the crude product was recrystallized from an appropriate solvent.

4,6-Dimethyl-2-oxo-1-(m-tolyl)-1,2-dihydropyrimidinium D-camphor-10-sulfonate (73)

(from ethyl acetate-hexane); IR: 3440, 1730, and 1625; PMR: 0.82 (s, 3H), 1.10 (s, 3H), 2.28 (s, 3H), 2.33 (s, 3H), 2.77 (s, 3H), 6.83 (s, 1H), and 7.1-7.3 (m, 4H).

1-(m-Methoxy)phenyl-4,6-dimethyl-2-oxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (74)

(from ethanol-hexane); IR: 3450, 1735, and 1620; PMR: 0.82 (s, 3H), 1.10 (s, 3H), 2.30 (s, 3H), 2.77 (s, 3H), 3.80 (s, 3H), 6.80 (s, 1H), and 7.1-7.3 (m, 4H).

4,6-Dimethyl-2-oxo-1-(o-tolyl)-1,2-dihydropyrimidinium D-camphor-10-sulfonate (75)

(from ethyl acetate-hexane); IR: 3470, 1740, and 1620; PMR: 0.80 (s, 3H), 1.08 (s, 3H), 2.08 (s, 3H), 2.22 (s, 3H), 2.78 (s, 3H), 6.58 (s, 1H), and 7.2-7.4 (m, 4H).

1-(o-Methoxy)phenyl-4,6-dimethyl-2-oxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (76)

(from ethyl acetate-hexane); IR: 3450, 1735, and 1610; PMR: 0.80 (s, 3H), 1.10 (s, 3H), 2.25 (s, 3H), 2.76 (s, 3H), 3.80 (s, 3H), 6.78 (s, 1H), and 7.0-7.4 (m, 4H).

1-(o-Ethyl)phenyl-4,6-dimethyl-2-oxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (77)

(from ethyl acetate-hexane); IR: 3450, 1730, and 1615; PMR: 0.80 (s, 3H), 1.07 (s, 3H), 1.33 (t, 3H, J=7.0 Hz), 2.18 (s, 3H), 2.75 (s, 3H), 6.87 (s, 1H), and 7.2-7.5 (m, 4H).

1-(o-Chloro)phenyl-4,6-dimethyl-2-oxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (78)

(from ethanol-ethyl acetate); IR: 3450, 1735, and 1620; PMR: 0.79 (s, 3H), 1.05 (s, 3H), 2.25 (s, 3H), 2.77 (s, 3H), 6.78 (s, 1H), and 7.3-7.5 (m, 4H).

4,6-Dimethyl-2-thioxo-1-(o-tolyl)-1,2-dihydropyrimidinium D-camphor-10-sulfonate (79)

(from ethyl acetate-hexane); IR: 3460 and 1735; PMR: 0.82 (s, 3H), 1.10 (s, 3H), 2.13 (s, 3H), 2.28 (s, 3H), 2.90 (s, 3H), 7.2-7.6 (m, 5H), and 12.80 (br. s, 1H).

1-(o-Methoxy)phenyl-4,6-dimethyl-2-thioxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (80)

(from ethyl acetate-hexane); IR: 3430 and 1740; PMR: 0.82 (s, 3H), 1.10 (s, 3H), 2.30 (s, 3H), 2.85 (s, 3H), 3.83 (s, 3H), 7.1-7.6 (m, 5H), and 12.72 (br. s, 1H).

1-(o-Ethyl)phenyl-4,6-dimethyl-2-thioxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (81)

(from ethyl acetate-hexane); IR: 3450 and 1740; PMR: 0.82 (s, 3H), 1.08 (s, 3H), 1.20 (t, 3H, J=7.0 Hz), 2.27 (s, 3H), 2.88 (s, 3H), 7.26 (s, 1H), 7.3-7.5 (m, 4H), and 12.25 (br. s, 1H).

1-(o-Ethoxy)phenyl-4,6-dimethyl-2-thioxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (82)

Table 43 Analytical Data of Pyrimidinium Salts

| Compd. No | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|
| 73 | $C_{23}H_{30}N_2O_5S$ | 61.85 | 6.79 | 6.05 | 61.86 | 6.77 | 6.27 |
| 74 | $C_{23}H_{30}N_2O_6S$ | 59.78 | 6.31 | 5.82 | 59.72 | 6.53 | 6.05 |
| 75 | $C_{23}H_{30}N_2O_5S$ | 62.21 | 6.81 | 5.88 | 61.86 | 6.77 | 6.27 |
| 76 | $C_{23}H_{30}N_2O_6S$ | 59.49 | 6.36 | 6.10 | 59.72 | 6.53 | 6.05 |
| 77 | $C_{24}H_{32}N_2O_5S$ | 62.47 | 6,86 | 5.86 | 62.58 | 7.00 | 6.08 |
| 78 | $C_{22}H_{27}N_2O_5SCl$ | 56.59 | 5.83 | 5.88 | 56.58 | 5.82 | 6.00 |
| 79 | $C_{23}H_{30}N_2O_4S_2$ | 60.03 | 6.57 | 6.14 | 59.71 | 6.53 | 6.05 |
| 80 | $C_{23}H_{30}N_2O_5S_2$ | 57.79 | 6.23 | 5.90 | 57.71 | 6.31 | 5.85 |
| 81 | $C_{24}H_{32}N_2O_4S_2$ | 60.60 | 6.66 | 5.89 | 60.47 | 6.76 | 5.87 |
| 82 | $C_{24}H_{32}N_2O_5S_2$ | 58.98 | 6.59 | 5.89 | 58.51 | 6.54 | 5.68 |
| 83 | $C_{22}H_{27}N_2O_4S_2Cl$ | 54.71 | 5.50 | 5.85 | 54.70 | 5.63 | 5.79 |
| 84 | $C_{23}H_{29}N_2O_4S_2Cl$ | 55.52 | 5.78 | 5.70 | 55.57 | 5.88 | 5.63 |

(from ethyl acetate-hexane); PMR: 0.82 (s, 3H), 1.10 (s, 3H), 1.27 (t, 3H, J=7.0 Hz), 2.30 (s, 3H), 2.85 (s, 3H), 7.1-7.6 (m, 5H), and 12.72 (br. s, 1H).

1-(o-Chloro)phenyl-4,6-dimethyl-2-thioxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (83)

(from ethanol-hexane); IR: 3440 and 1740; PMR: 0.80 (s, 3H), 1.07 (s, 3H), 2.27 (s, 3H), 2.83 (s, 3H), 6.97 (s, 1H), 7.3-7.8 (m, 4H), and 12.72 (br. s, 1H).

1-(2-Methyl-3-chloro)phenyl-4,6-dimethyl-2-thioxo-1,2-dihydropyrimidinium D-camphor-10-sulfonate (84)

(from ethyl acetate-hexane); IR: 3440 and 1735; PMR: 0.82 (s, 3H), 1.08 (s, 3H), 2.15 (s, 3H), 2.28 (s, 3H), 2.88 (s, 3H), 7.28 (s, 1H), 7.3-7.6 (m, 3H), and 12.17 (br. s, 1H).

Analytical data for these compounds are presented in Table 43.

## Antiinflammatory Test

Male Wister rats weighing 120 to 150 g were used. They were fasted for 18 hr before the experiment, but water was given freely. The agents tested were administered per os 1 hr before the carrageenin treatment. After 1 hr, the subplantar injection of 0.05 ml of 1% carrageenin (Picnin-A® Pasco International) was carried out. The volume of the injected hind paw was measured prior to the injection, and 3 and 4 after the injection. The volume of the rat hind paw was measured by Ugo-Basil. The percent inhibition of edema

induced by each agent was calculated for each animal group with respect to its vehicle-tested control group. The percent inhibitation is listed in Table 13.

## Formation of Pyrimidinium Salts with Methyl Iodide

The mixture of 2(1H)-pyrimidinone (1 mmol) and methyl iodide (10 mmol) was heated at 120 °C for 8 hr in a sealed tube. The crude salt was filtered off and recrystallized from an appropriate solvent.

1,2-Dihydro-3,4,6-trimethyl-2-oxo-1-phenylpyrimidinium iodide (90)

mp 182 °C (decomp., from ethyl acetate-hexane); IR: 3480, 1720, 760, and 750; PMR: 1.97 (s, 3H), 2.48 (s, 3H), 3.42 (s, 3H), 6.77 (s, 1H), and 7.27 (m, 5H).

4,6-Dimethyl-2-methylthio-1-phenylpyrimidinium iodide (91)

(from ethyl acetate-hexane); IR: 2990, 1615, 1280, 760, and 690; PMR: 2.48 (s, 3H), 2.62 (s, 3H), 2.78 (s, 3H), 7.40 (s, 1H), and 7.7-7.9 (m, 5H).

## Reaction of 4,6-Dimethyl-1-phenyl-2(1H)-pyrimidinone (32) with Alkyl Halides

Compound 32 (1 mmol) was stirred for 1 hr in dry DMF (10 ml) in the presence of sodium hydride (60% in oil, 1.5 mmol), and alkyl halide (6 mmol) in dry DMF (5 ml) was added

dropwise to the solution in an ice-MeOH bath. After stirring for another 1 hr, the reaction mixture was poured into cold water, and extracted with dichloromethane. The crude product was chromatographed on silica gel with chloroform-acetone-ethanol (100:20:4) mixture.

6-(3-butenyl)-4-methyl-1-phenyl-2(1H)-pyrimidinone (92)

PMR: 2.0-2.3 (m, 4H), 2.38 (s, 3H), 4.7-5.7 (m, 3H), 6.10 (s, 1H), and 7.0-7.5 (m, 5H).

4-Methyl-6-phenethyl-1-phenyl-2(1H)-pyrimidinone (93)

mp 163-164 °C (from benzene-hexane); IR: 3060, 1660, 760, and 700; PMR: 2.37 (s, 3H), 2.4-2.9 (m, 4H), 6.15 (s, 1H), and 6.7-7.6 (m, 10H).

## Conversion of Thiocarbonyl into Carbonyl Group

2-Methylthio-4-methyl-1,6-diphenylpyrimidinium iodide (94)

The mixture of compound 59 (1 mmol) and methyl iodide (10 mmol) was heated at 120 °C in a sealed tube for 8 hr. The product was recrystallized from ethanol and mp 234 °C (decomp.), yield 85%. IR: 3010, 1260, 1235, 760, and 740; PMR: 2.83 (s, 3H), 2.98 (s, 3H), 7.4-7.8 (m, 10H), and 8.15 (s, 1H). Found: C 51.48, H 3.92, N 6.82. $C_{18}H_{17}IN_2S$ requires C 51.43, H 4.07, N 6.66%.

Hydrolysis of Pyrimidinium Iodide (94) The compound 94 (0.2 mmol) was treated with sodium methoxide (0.9 mmol) in

methanol (20 ml) at room temperature for 3 hr. After diluting with water, the product, which was extracted with dichloromethane, was identified with compound 55 by spectral data and the mixed melting[113].

Conversion of Thiocarbonyl into Carbonyl Group 2(1H)-Pyrimidinethione (1 mmol) was dissolved in methanol (20 ml) in the presence of sodium methoxide (4 mmol). To the solution, methyl iodide (10 ml) was added at room temperature. After stirring for 3 hr, the reaction mixture was poured into water and extracted with dichloromethane. The crude product was chromatographed on silica gel with chloroform-acetone-ethanol (100:20:4).

6-(p-Methoxy)phenyl-4-methyl-1-phenyl-2(1H)-pyrimidinone (95) mp 162 °C (decomp., from benzene-hexane); IR: 1660; PMR: 2.20 (s, 3H), 2.45 (s, 3H), 6.35 (s, 1H), and 6.9-7.6 (m, 9H). Found: C 78.52, H 5.79, N 10.04. $C_{18}H_{16}N_2O$ requires C 78.23, H 5.83, N 10.13%.

1-(p-Chloro)phenyl-4-methyl-1-phenyl-2(1H)-pyrimidinone (96) mp 164 °C (decomp., from benzene-hexane); IR: 1650; PMR: 2.50 (s, 3H), 6.33 (s, 1H), and 6.8-7.5 (m, 9H). Found: C 69.10, H 4.34, N 9.26. $C_{17}H_{13}N_2OCl$ requires C 68.80, H 4.41, N 9.44%.

## Reaction with Nucleophiles

## Reaction with Amines

Reaction with Ammonia  2(1H)-Pyrimidinethione (2 mmol) was added to the solution of absolute ethanol (10 ml) saturated with ammonia. The mixture was heated at 85 °C for 20 hr in a sealed tube. The reaction mixture was poured into water, extracted with dichloromethane, and then the extract was dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with benzene-ethyl acetate (5:1) mixture, and recrystallized from benzene-hexane mixture.

4-Methyl-2-methylamino-6-phenylpyrimidine (98)

IR: 3280, 1630, and 1600; PMR: 2.33 (s, 3H), 3.02 (d, 3H, J=5.0 Hz), 6.83 (s, 1H), and 7.2-8.2 (m,5H).

4,6-Dimethyl-2-(p-toluidino)pyrimidine (99)

IR: 3230, 1605, and 1580; PMR: 2.31 (s, 3H), 2.34 (s, 6H), 6.49 (s, 1H), and 7.0-7.7 (m, 4H). Found: C 72.94, H 7.08, N 19.75. $C_{13}H_{15}N_3$ requires C 73.20, H 7.08, N 19.70%.

2-Anilino-4-methyl-6-phenylpyrimidine (100)

IR: 3370, 1610, 1600, and 1580; PMR: 2.45 (s, 3H), 7.01 (s, 1H), and 7.1-8.2 (m, 11H). Found: C 78.18, H 5.77, N 16.13. $C_{17}H_{15}N_3$ requires C 78.13, H 5.78, N 16.07%.

2-Anilino-6-(p-chloro)phenyl-4-methylpyrimidine (101)

IR: 3360, 1590, and 1520; PMR: 2.45 (s, 3H) and 7.0-8.2 (m, 10H). Found: C 69.35, H 4.74, N 14.14. $C_{17}H_{14}N_3Cl$ requires C 69.03, H 4.77, N 14.20%.

Reaction with Alkyl Amines To the mixture of 2(1H)-pyrimidinethione (3 mmol) and methylamine (18 mmol, 40% aqueous solution) in methanol (30 ml) was added a small excess of silver perchlorate. The mixture was stirred at room temperature overnight. The black precipitate of silver sulfide ($Ag_2S$) was removed by filtration, and the filtrate was evaporated under reduced pressure. The crude product was purified by recrystallization from ethanol.

2-Anilino-1,4,6-trimethylpyrimidinium perchlorate (105)

IR: 3360, 1620, 1600, and 1560; PMR (DMSO-$d_6$): 2.42 (s, 3H), 2.67 (s, 3H), 3.88 (s, 3H), 7.01 (s, 1H), and 7.2-7.6 (m, 5H).

2-Anilino-1-ethyl-4,6-dimethylpyrimidinium perchlorate (106)

IR: 3320, 1625, 1600, and 1560; PMR (DMSO-$d_6$): 1.48 (t, 3H, J=7.0 Hz), 2.39 (s, 3H), 2.70 (s, 3H), 4.48 (q, 2H, J=7.0 Hz), 7.09 (s, 1H), and 7.2-7.6 (m, 5H).

1,4,6-Trimethyl-2-(p-toluidino)pyrimidinium perchlorate (107)

IR: 3330, 1630, 1600, and 1560; PMR (DMSO-$d_6$): 2.38 (s, 3H), 2.42 (s, 3H), 2.66 (s, 3H), 3.86 (s, 3H), 7.03 (s, 1H), and 7.2-7.4 (m, 4H).

1,4,6-Trimethyl-2-(o-methoxy)anilinopyrimidinium perchlorate (108)

IR: 3260, 1600, 1580, and 1540; PMR (DMSO-$d_6$): 2.36 (s, 3H), 2.63 (s, 3H), 3.84 (s, 3H), 4.69 (s, 3H), and 6.9-7.5 (m, 5H).

2-Anilino-1,4-dimethyl-6-phenylpyrimidinium perchlorate (109)

IR: 3305, 1620, 1600, and 1570; PMR ($CD_3OD$): 2.51 (s, 3H), 3.80 (s, 3H), 6.88 (s, 1H), and 7.2-7.7 (m, 10H).

2-Anilino-1-ethyl-4-methyl-6-phenylpyrimidinium perchlorate (110)

IR: 3310, 1635, 1600, and 1560; PMR (DMSO-$d_6$): 1.30 (t, 3H, J=7.0 Hz), 2.48 (s, 3H), 4.28 (q, 2H, J=7.0 Hz), 7.09 (s, 1H), and 7.3-7.8 (m, 10H).

2-Anilino-1,4-dimethyl-6-(p-tolyl)pyrimidinium perchlorate (111)

IR: 3280, 1620, 1560, and 1560; PMR (DMSO-$d_6$): 2.49 (s, 3H), 2.55 (s, 3H), 4.80 (s, 3H), 6.90 (s, 1H), and 7.3-7.7 (m, 9H).

2-Anilino-6-(p-methoxy)phenyl-1,4-dimethylpyrimidinium perchlorate (112)

IR: 3285, 1620, 1605, and 1560; PMR (DMSO-$d_6$): 2.43 (s, 3H), 3.72 (s, 3H), 3.86 (s, 3H), and 6.9-7.7 (m, 10H).

2-Anilino-6-(p-chloro)phenyl-1,4-dimethylpyrimidinium perchlorate (113)

IR: 3280, 1625, 1600, and 1560; PMR (DMSO-$d_6$): 2.44 (s, 3H), 3.69 (s, 3H), 6.83 (s, 1H), and 7.3-7.7 (m, 9H).

Analytical data for these compounds are presented in Table 44.

Acid Hydrolysis of Pyrimidinium Perchlorates The mixture of pyrimidinium perchlorate (2 mmol) and concentrated hydrochloric acid (10 ml) was heated at 160 °C in a sealed tube for 1 hr. The reaction mixture was neutralized with aqueous sodium hydroxide, extracted with dichloromethane, and then

Table 44 Analytical Data of Pyrimidinium Perchlorates

| Compd. No | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|
| 105 | $C_{13}H_{16}ClN_3O_4$ | 49.75 | 5.11 | 13.46 | 49.76 | 5.14 | 13.46 |
| 106 | $C_{14}H_{18}ClN_3O_4$ | 51.18 | 5.51 | 12.70 | 51.30 | 5.53 | 12.82 |
| 107 | $C_{14}H_{18}ClN_3O_4$ | 51.51 | 5.51 | 12.89 | 51.30 | 5.53 | 12.82 |
| 108 | $C_{14}H_{18}ClN_3O_5$ | 49.09 | 5.24 | 12.29 | 48.91 | 5.27 | 12.22 |
| 109 | $C_{18}H_{18}ClN_3O_4$ | 57.61 | 4.87 | 11.05 | 57.52 | 4.82 | 11.18 |
| 110 | $C_{19}H_{20}ClN_3O_4$ | 58.38 | 5.15 | 10.71 | 58.53 | 5.17 | 10.77 |
| 111 | $C_{19}H_{20}ClN_3O_4$ | 58.36 | 5.15 | 10.76 | 58.53 | 5.17 | 10.77 |
| 112 | $C_{19}H_{20}ClN_3O_5$ | 56.42 | 4.95 | 10.44 | 56.23 | 4.96 | 10.35 |
| 113 | $C_{18}H_{17}Cl_2N_3O_4$ | 52.44 | 4.13 | 10.08 | 56.69 | 4.17 | 10.24 |

the extract was dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with chloroform-acetone-ethanol (100:20:4) mixture.

1-Ethyl-4-methyl-6-phenyl-2(1H)-pyrimidinone (114)

IR: 1640 and 1600; PMR: 1.19 (t, 3H, J=7.0 Hz), 2.37 (s, 3H), 3.91 (q, 2H, J=7.0 Hz), 6.09 (s, 1H), and 7.1-7.7 (m, 5H). Found: C 72.91, H 6.60, N 13.11. $C_{13}H_{14}N_2O$ requires C 72.87, H 6.58, N 13.07%.

6-(p-Methoxy)phenyl-1,4-dimethyl-2(1H)-pyrimidinone (115)

IR: 1645 and 1600; PMR: 2.34 (s, 3H), 3.39 (s, 3H), 4.82 (s, 3H), 6.12 (s, 1H), and 6.8-7.4 (m, 4H). Found: C 67.89, H 6.10, N 12.02. $C_{13}H_{14}N_2O_2$ requires C 67.80, H 6.12, N 12.16%.

6-(p-Chloro)phenyl-1,4-dimethyl-2(1H)-pyrimidinone (116)

IR: 1690 and 1595; PMR: 2.39 (s, 3H), 3.37 (s, 3H), 6.18 (s, 1H), and 7.1-7.9 (m, 4H). Found: C 61.60, H 4.69, N 11.98. $C_{12}H_{11}ClN_2O$ requires C 61.41, H 4.72, N 11.93%.

Reaction with Hydroxylamine A mixture of 2(1H)-pyrimidinethione (2 mmol), hydroxylamine hydrochloride (2.2 mmol), and sodium hydroxide (4.4 mmol) in absolute ethanol (30 ml) was refluxed for 2 hr. The reaction mixture was poured into water, and extracted with dichloromethane, then the extract was dried over anhydrous magnesium sulfate. The crude products were chromatographed on silica gel with benzene-ethyl acetate (4:1) for compounds 122-124 or with

chloroform-acetone-ethanol (100:20:4) for compounds 117-121.

2-Anilino-4,6-dimethylpyrimidine 1-oxide (117)

IR: 3240, 1600, 1445, 1245, 1205, and 1165; UV: 246 (4.32), 283 (4.30), 330 (3.70); PMR: 2.41 (s, 3H), 2.52 (s, 3H), 6.60 (s, 1H), 7.1-7.6 (m, 3H), 7.6-7.9 (m, 2H) and 9.7 (br. s, 1H); CMR: 17.7 (q), 23.6 (q), 110.9 (d), 119.6 (d), 123.6 (d), 128.9 (d), 137.7 (s), 149.9 (s), 152.8 (s), and 154.1 (s). Found: C 66.98, H 6.02, N 19.58. $C_{12}H_{13}N_3O$ requires C 66.95, H 6.08, N 19.52%.

4,6-Dimethyl-2-methylaminopyrimidine 1-oxide (118)

IR: 3270, 1610, 1430, 1160, and 1125; UV: 231 (4.29), 254 (3.81), 327 (3.81); PMR: 2.30 (s, 3H), 2.42 (s, 3H), 3.07 (d, 3H, J=5.0 Hz), 6.38 (s, 1H), and 7.4 (br. s, 1H). Found: C 54.82, H 7.17, N 27.30. $C_7H_{11}N_3O$ requires C 54.88 H 7.23, N 27.23%.

4,6-Dimethyl-2-(p-toluidino)pyrimidine 1-oxide (119)

IR: 3230, 1595, 1560, 1245, 1205, and 1170; UV: 243 (4.15), 282 (4.31), 322 (3.64); PMR: 2.32 (s, 3H), 2.40 (s, 3H), 2.51 (s, 3H), 6.54 (s, 1H), 7.0-7.4 (m, 2H), 7.5-7.8 (m, 2H), and 9.5 (br. s, 1H). Found: C 68.00, H 6.61, N 18.24. $C_{13}H_{15}N_3O$ requires C 68.10, H 6.59, N 18.32%.

4,6-Dimethyl-2-(o-toluidino)pyrimidine 1-oxide (120)

IR: 3240, 1580, 1260, 1220, 1165, and 740; UV: 242 (4.20), 279 (4.18), 327 (3.70); PMR: 2.38 (s, 3H), 2.50 (s, 3H), 6.54 (s, 1H), 7.0-7.5 (m, 3H), 8.1-8.4 (m, 1H), and 9.6 (br. s, 1H). Found: C 67.89, H 6.58, N 18.36. $C_{13}H_{15}N_3O$

requires C 68.10, H 6.59, N 18.32%.

2-(o-Ethyl)anilino-4,6-dimethylpyrimidine 1-oxide (121)

IR: 3130, 1590, 1555, 1440, 1210, and 1165; UV: 242 (4.16), 278 (4.16), 324 (3.61); PMR: 1.30 (t, 3H, J=7.0 Hz), 2.33 (s, 3H), 2.50 (s, 3H), 2.77 (q, 2H, J=7.0 Hz), 6.50 (s, 1H), 7.0-7.5 (m, 3H), 8.2-8.4 (m, 1H), and 9.8 (br. s, 1H). Found: C 68.98, H 6.99, N 17.19. $C_{14}H_{17}N_3O$ requires C 69.11, H 7.04, N 17.27%.

2-Anilino-4-methyl-6-phenylpyrimidine 1-oxide (122)

IR: 3240, 1580, 1560, 1440, 1140, and 1100; UV: 239 (4.32), 280 (4.44), 354 (3.56); PMR: 2.47 (s, 3H), 6.70 (s, 1H), 7.0-8.2 (m, 10H), and 9.9 (br. s, 1H). Found: C 73.55, H 5.42, N 15.12. $C_{17}H_{15}N_3O$ requires C 73.62, H 5.45, N 15.15%.

2-Anilino-4-methyl-6-(p-tolyl)pyrimidine 1-oxide (123)

IR: 3140, 1585, 1560, 1140, 1100, and 805; UV: 243 (4.18), 282 (4.47), 352 (3.65); PMR: 2.40 (s, 3H), 2.42 (s, 3H), 6.74 (s, 1H), 7.1-7.6 (m, 7H), 7.7-8.0 (m, 2H), and 9.9 (br. s, 1H). Found: C 74.06, H 5.81, N 14.41. $C_{18}H_{17}N_3O$ requires C 74.20, H 5.88, N 14.42%.

2-Anilino-6-(p-chloro)phenyl-4-methylpyrimidine 1-oxide (124)

IR: 3200, 1590, 1560, 1140, 1085, 815, and 750; UV: 243 (4.29), 280 (4.48), 357 (3.54); PMR: 2.42 (s, 3H), 6.70 (s, 1H), 7.0-8.1 (m, 9H), and 9.9 (br. s, 1H). Found: C 65.30, H 4.56, N 13.44. $C_{17}H_{14}N_3ClO$ requires C 65.49, H 4.52, N 13.47%.

The reaction of 2(1H)-pyrimidinones with hydroxylamine was carried out in the manner described above. The products 125-129 were identified by comparison with authentic samples (spectral data and mixed melting point). (Table 23)

Deoxygenation of Pyrimidine 1-Oxide (117) Raney nickel was prepared *in situ* according to the following procedure. NaOH pellet (5 g) was added within 10 min to the mixture of nickel-aluminum alloy (Wako Pure Chemical Industries LTD, about 50%, 4 g) in distilled water (60 ml) with vigorous stirring at room temperature. After 15 min, the reaction mixture was immersed in oil bath (bath temperature 70 °C) for 20 min, and then the alkaline solution was decanted. The nickel was washed ten times by suspension in distilled water and decantation. The washing procedure was repeated five times with methanol.

The reaction mixture of compound 117 (1 mmol) in methanol (30 ml) was deoxygenated in the presence of Raney nickel under hydrogen at room temperature. After removal of the catalyst, the solvent was evaporated off. The crude product was recrystallized from hexane to give 97 (75% yield). The product 97 was identical (spectral data and mixed melting point) with an authentic sample[70),142)].

## Reaction with Organometallic Reagents

Reaction with Alkyl-lithium Alkyl-lithium (10 mmol) was prepared from alkyl iodide (10 mmol) and lithium wire (25 mmol) in anhydrous ether (20 ml) under an argon atmosphere in an ice-bath. To this solution, 2(1H)-pyrimidinone (3 mmol) was added and the mixture was stirred for 5 hr at room temperature. Excess of alkyl-lithium was destroyed by the dropwise addition of water. The reaction mixture was extracted with dichloromethane and dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with chloroform-acetone-ethanol (100:10:2) in the case of 2(1H)-pyrimidinone, and with chloroform-benzene-ethyl acetate (4:4:1) in the case of 2(1H)-pyrimidinethione.

3,4-Dihydro-4-ethyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (147)

mp 194-195 °C (decomp., from ethyl acetate): IR: 3180, 2960, 1685, 1230, 760, and 700; PMR: 1.02 (t, 3H, J=6.0 Hz), 1.33 (s, 3H), 1.52 (s, 3H), 4.70 (br. s, 1H), and 7.2-7.5 (m, 5H). Found: C 68.55, H 7.4, N 11.4. $C_{14}H_{18}N_2S$ requires C 68.25, H 7.36, N 11.37%.

3,4-Dihydro-4-isopropyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (149)

mp 182-183 °C (decomp., from ethyl acetate-hexane); IR: 3180, 2960, 1685, 760, and 700; PMR: 0.92 (d, 3H, J=6.0 Hz), 1.05 (d, 3H, J=6.0 Hz), 1.32 (s, 3H), 1.52 (s, 3H), 4.73 (br. s, 1H), and 7.2-7.5 (m, 5H). Found: C 69.2, H 7.8, N 10.7. $C_{15}H_{20}N_2S$ requires C 69.18, H 7.74, N 10.75%.

Reaction with Alkyl Grignards 2(1H)-Pyrimidinone (1 mmol) was added to the solution of methylmagnesium iodide (10 mmol) in anhydrous ether (20 ml) and the mixture was stirred for 6 hr. The reaction mixture was washed with cold water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with chloroform-acetone-ethanol (100:20:4)[(100:10:2) in the case of 2(1H)-pyrimidinones], and with chloroform-benzene-ethyl acetate (4:4:1)[(4:10:1) in the case of 2(1H)-pyrimidinethiones].

3,6-Dihydro-4,6,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (137)

mp 191-192 °C (from benzene-hexane); IR: 3200, 2960, 1660, and 760; UV: 233 (3.66); PMR: 1.18 (s, 6H), 1.70 (d, 3H, J=0.6 Hz), 4.45 (br. s, 1H), and 7.2-7.5 (m, 5H). Found: C 72.2, H 7.4, N 13.0. $C_{13}H_{16}N_2O$ requires C 72.19, H 7.45, N 12.95%.

3,4-Dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (138)

mp 163 °C (Lit.[27] 162-164 °C) (from ethyl acetate-hexane); IR: 3220, 2960, 1660, 1395, 1380, 760, and 695; UV: 229 (3.83); PMR: 1.30 (s, 6H), 1.53 (d, 3H, J=0.6 Hz), 4.62 (br. s, 1H), 5.02 (br. s, 1H), and 7.1-7.4 (m, 5H). Found: C 72.0, H 7.4, N 13.1. $C_{13}H_{16}N_2S$ requires C 72.19, H 7.45, N 12.95%.

3,6-Dihydro-6-ethyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (139)

mp 143-144 °C (from benzene-hexane); IR: 3220, 2960, 1660,

and 755; PMR: 1.08 (t, 3H, J=6.0 Hz), 1.33 (s, 3H), 1.73 (s, 3H), 4.25 (br. s, 1H), and 7.0-7.2 (m, 5H). Found: C 72.9, H 7.7, N 12.2. $C_{14}H_{18}N_2O$ requires C 73.01, H 7.87, N 12.16%.

3,4-Dihydro-4-ethyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (140)

mp 168 °C (from benzene-hexane); IR: 3230, 2960, 1660, and 755; PMR: 1.00 (t, 3H, J=6.0 Hz), 1.28 (s, 3H), 1.53 (s, 3H), 4.48 (br. s, 1H), 4.76 (br. s, 1H), and 7.0-7.2 (m, 5H). Found: C 72.5, H 7.9, N 12.0. $C_{14}H_{18}N_2O$ requires C 73.01, H 7.87, N 12.16%.

3,4-Dihydro-4-isopropyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (141)

mp 202 °C (from benzene-hexane); IR: 3200, 2960, 1690, 1600, 760, and 690; PMR: 0.97 (d, 6H, J=6.0 Hz), 1.27 (s, 3H), 1.52 (s, 3H), 4.50 (br. s, 1H), 4.83 (br. s, 1H), and 7.0-7.2 (m, 5H). Found: C 73.55, H 8.3, N 11.5. $C_{15}H_{20}N_2O$ requires C 73.73, H 8.25, N 11.46%.

3,6-Dihydro-6-t-butyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (142)

mp 191 °C (from benzene-hexane); IR: 3200, 2960, 1700, 1650, 1380, and 760; PMR: 0.98 (s, 9H), 1.17 (s, 3H), 1.72 (s, 3H), 4.37 (br. s, 1H), 6.9-7.3 (m, 5H). Found: C 74.2, H 8.6, N 10.7. $C_{16}H_{22}N_2O$ requires C 74.38, H 8.58, N 10.84%.

3,4-Dihydro-4-t-butyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (143)

mp 139 °C (from hexane); IR: 3240, 2960, 1690, 1660, 760, and 680; PMR: 0.96 (s, 9H), 1.23 (s, 3H), 1.52 (s, 3H), 4.60 (br. s, 1H), 5.07 (br. s, 1H), and 7.0-7.3 (m, 5H). Found: C 74.6, H 8.65, N 10.95. $C_{16}H_{22}N_2O$ requires C 74.38, H 8.58, N 10.84%.

3,6-Dihydro-4,6,6-trimethyl-1-phenyl-2(1H)-pyrimidinethione (144)[207]

mp 215-223 °C (from ethyl acetate); PMR: 1.22 (s, 6H), 1.78 (d, 3H, J=0.6 Hz), 4.50 (br. s, 1H), and 7.1-7.5 (m, 5H). Found[for a mixture of 144 and 145]: C 67.15, H 6.95, N 11.95. $C_{13}H_{16}N_2S$ requires C 67.20, 6.94, N 12.05%.

3,6-Dihydro-6-ethyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (146)[207]

mp 170-179 °C (decomp., from ethyl acetate); PMR: 1.02 (t, 3H, J=6.0 Hz), 1.13 (s, 3H), 1.85 (d, 3H, J=0.6 Hz), 4.50 (br. s, 1H), and 7.2-7.5 (m, 5H). Found[for a mixture of 146 and 147]: C 68.25, H 7.35, N 11.3. $C_{14}H_{18}N_2S$ requires C 68.25, H 7.36, N 11.37%.

3,6-Dihydro-6-isopropyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (148)[207]

mp 197-203 °C (decomp., from benzene-hexane); PMR: 0.80 (d, 6H, J=6.0 Hz), 1.15 (s, 3H), 1.83 (s, 3H), 4.48 (br. s, 1H), 7.2-7.5 (m, 5H), and 8.27 (br. s, 1H). Found[for a mixture of 148 and 149]: C 69.25, H 7.8, N 10.7. $C_{15}H_{20}N_2S$ requires C 69.18, H 7.74, N 10.75%.

3,6-Dihydro-6-t-butyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimi-

dinethione (150)

mp 167-168 °C (decomp., from ethyl acetate-hexane); IR: 3240, 2960, 1710, 1240, and 710; PMR: 1.03 (s, 9H), 1.18 (s, 3H), 1.85 (s, 3H), 4.60 (br. s, 1H), 7.1-7.5 (m, 5H), and 8.43 (br. s, 1H). Found: C 69.8, H 7.9, N 10.1. $C_{16}H_{22}N_2S$ requires C 70.02, H 8.08, N 10.20%.

3,4-Dihydro-4-t-butyl-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (151)

mp 180 °C (decomp., from benzene-hexane); IR: 3180, 2960, 1680, 1600, and 760; PMR: 1.01 (s, 9H), 1.28 (s, 3H), 1.53 (s, 3H), 4.75 (br. s, 1H), and 7.1-7.4 (m, 5H). Found: C 70.0, H 8.0, N 10.2. $C_{16}H_{22}N_2S$ requires C 70.02, H 8.08, N 10.20%.

3,6-Dihydro-1-methyl-6-phenylethynyl-2(1H)-pyrimidinone (152)

mp 134-135 °C (from ethyl acetate-hexane); IR: 3220, 2940, 1680, and 750; PMR: 3.04 (s, 3H), 4.6-5.0 (m, 2H), 6.0-6.3 (d. d, 1H, J=7.0 and 4.8 Hz), 7.2-7.5 (m, 5H), and 8.50 (br. s, 1H). Found: C 73.7, H 5.65, N 13.2. $C_{13}H_{12}N_2O$ requires C 73.56, H 5.69, N 13.19%.

3,6-Dihydro-6-methyl-1-phenyl-2(1H)-pyrimidinone (153)

mp 140.5 °C (decomp., from ethyl acetate-hexane); IR: 3220, 2960, 1650, 1190, and 760; PMR: 1.17 (d, 3H, J=6.0 Hz), 4.2-4.9 (m, 2H), 5.9-6.2 (d. d, 1H, J=8.0 and 5.6 Hz), 7.2-7.5 (m, 5H), and 8.35 (br. s, 1H). Found: C 69.95, H 6.4, N 14.8. $C_{11}H_{12}N_2O$ requires C 70.19, H 6.42, N 14.88%.

3,6-Dihydro-4,6,6-trimethyl-1-(p-tolyl)-2(1H)-pyrimidi-

none (154)

mp 211-212 °C (from ethyl acetate-hexane); IR: 3200, 2960, 1710, 1660, 1400, 810, and 740; PMR: 1.20 (s, 6H), 1.75 (d, 3H, J=0.6 Hz), 2.36 (s, 3H), 4.47 (br. s, 1H), and 7.1-7.2 (m, 4H). Found: C 73.6, H 7.95, N 12.15. $C_{14}H_{18}N_2O$ requires C 73.01, H 7.87, N 12.16%.

3,4-Dihydro-4,4,6-trimethyl-1-(o-tolyl)-2(1H)-pyrimidinone (155)

mp 193 °C (from ethyl acetate-hexane); IR: 3220, 2960, 1700, 1670, 1510, 805, and 750; PMR: 1.32 (s, 6H), 1.51 (d, 3H, J=0.6 Hz), 2.35 (s, 3H), 4.64 (br. s, 1H), 5.04 (br. s, 1H), and 7.1-7.2 (m, 4H). Found: C 73.3, H 7.9, N 12.5. $C_{14}H_{18}N_2O$ requires C 73.01, H 7.87, N 12.16%.

3,6-Dihydro-6,6-dimethyl-1,4-diphenyl-2(1H)-pyrimidinone (156)

mp 196-197 °C (from ethyl acetate); IR: 3220, 2980, 1640, 1410, 760, and 740; PMR: 1.33 (s, 6H), 4.93 (br. s, 1H), and 7.0-7.5 (m, 10H). Found: C 77.7, H 6.45, N 10.05. $C_{18}H_{18}N_2O$ requires C 77.66, H 6.51, N 10.06%.

3,4-Dihydro-4,4-dimethyl-1,6-diphenyl-2(1H)-pyrimidinethione (157)

mp 206-207 °C (decomp., from benzene-hexane); IR: 3200, 2980, 1680, 1540, 1340, 1200, and 700; PMR: 1.48 (s, 6H), 5.10 (br. s, 1H), and 7.0-7.3 (m, 10H). Found: C 73.5, H 6.10, N 9.55. $C_{18}H_{18}N_2S$ requires C 73.43, H 6.16, N 9.51%.

## Reaction with Metal Hydride Complexes

Method A To a solution of 2(1H)-pyrimidinone (2 mmol) and methyl borate (6 mmol) in ethanol on an ice-water bath was added $NaBH_4$ (4 mmol) and the mixture was then stirred for 2 hr at room temperature. The reaction mixture was diluted with water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate.

3,6-Dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (159) mp 134-135 °C (from benzene-hexane); IR: 3200, 2960, 1700, 1660, 760, and 690; UV: 209 (4.10); PMR: 1.13 (d, 3H, J=6.0 Hz), 1.73 (s, 3H), 4.2-4.7 (m, 2H), and 7.2-7.5 (m, 5H). Found: C 71.4, H 6.9, N 13.65. $C_{12}H_{14}N_2O$ requires C 71.26, H 6.97, N 13.85%.

3,6-Dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (164) mp 119-120 °C (from benzene-hexane); IR: 3200, 1705, 1280, 765, and 700; PMR: 1.18 (d, 3H, J=6.0 Hz), 1.77 (s, 3H), 4.1-4.4 (m, 1H), 4.6-4.8 (m, 1H), 7.2-7.5 (m, 5H), and 8.63 (br. s, 1H). Found: C 66.4, H 6.35, N 12.55. $C_{12}H_{14}N_2S$ requires C 66.01, H 6.46, N 12.83%.

Method B To a solution of 2(1H)-pyrimidinone (1 mmol) and sodium hydroxide (5 mmol) in methanol (20 ml) was added $NaBH_4$ (10 mmol) and the mixture was stirred overnight at room temperature.

Tetrahydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (161)

mp 178-179 °C (from benzene); IR: 3200, 3040, 2960, 1650, 760, and 680; UV: 209 (3.78) and 229 (3.59); PMR: 0.93 (d, 3H, J=6.0 Hz), 1.13 (d, 3H, J=6.0 Hz), 1.4-2.1 (m, 2H), 3.3—4.1 (m, 2H), 5.53 (br. s, 1H), and 7.2-7.5 (m, 5H). Found: C 70.9, H 7.9, N 13.6. $C_{12}H_{16}N_2O$ requires C 70.55, H 7.89, N 13.71%.

Tetrahydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (166)

mp 175-176 °C (from ethyl acetate); IR: 3200, 1520, 1240, 760, and 680; PMR: 0.93 (d, 3H, J=6.0 Hz), 1.23 (d, 3H, J=6.0 Hz), 1.5-2.3 (m, 2H), 3.3-4.2 (m, 2H), and 7.0-7.6 (m, 5H). Found: C 65.65, H 7.25, N 12.5. $C_{12}H_{16}N_2S$ requires C 65.41, H 7.31, N 12.71%.

Method C To a solution of 2(1H)-pyrimidinone (2 mmol) in dry ether (20 ml) was added $LiAlH_4$ (2 mmol) under an argon atmosphere and the mixture was stirred for 2 hr at room temperature. The reaction mixture was diluted with cold water and extracted with dichloromethane, and the organic layer was concentrated. The residue was treated with $NaBH_4$ as Method B. Compound 32 gave compound 161 and

3,4-dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (160)

mp 119-120 °C (from benzene-hexane); IR: 3220, 1695, 1660, 760, and 690; UV: 220 (4.34) and 254 (4.30); PMR: 1.27 (d, 3H, J=6.0 Hz), 1.52 (s, 3H), 4.1-4.3 (m, 1H), 4.6-4.8 (m, 1H), 5.90 (br. s, 1H), and 7.2-7.6 (m, 5H). Found: C 71.15, H 6.95, N 13.85. $C_{12}H_{14}N_2O$ requires C 71.26, H 6.97, N

13.85%

Compound 36 gave compound 166 and 3,4-dihydro-4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (165)

mp 140.5 °C (decomp., from ethyl acetate); IR: 3200, 1680, 1530, 1220, 760, and 690; PMR: 1.30 (d, 3H, J=6.0 Hz), 1.48 (s, 3H), 4.1-4.3 (m, 1H), 4.8-5.0 (m, 1H), 7.2-7.5 (m, 5H), and 7.90 (br. s, 1H). Found: C 65.8, H 6.4, N 12.8. $C_{12}H_{14}N_2S$ requires C 66.01, H 6.46, N 12.83%.

Method D To a solution of 2(1H)-pyrimidinone (2 mmol) in dry ether (15 ml) was added, slowly, $LiAlH_4$ (1 mmol) under an argon atmosphere, and the mixture was stirred for 3 hr at room temperature.

3,6-Dihydro-6-methyl-1,4-diphenyl-2(1H)-pyrimidinone (167)

mp 179-180 °C (from benzene-hexane); IR: 3200, 3080, 2960, 1655, 1285, and 700; PMR: 1.25 (d, 3H, J=6.0 Hz), 4.4-4.6 (m, 1H), 5.0-5.2 (m, 1H), and 7.2-7.5 (m, 10H). Found: C 77.1, H 6.05, N 10.4. $C_{17}H_{16}N_2O$ requires C 77.24, H 6.10, N 10.59%.

3,4-Dihydro-4-methyl-1,6-diphenyl-2(1H)-pyrimidinone (168)

mp 184-185 °C (from ethyl acetate); IR: 3240, 1680, 1655, 1410, 755, and 700; PMR: 1.37 (d, 3H, J=6.0 Hz), 4.1-4.5 (m, 1H), 5.0-5.2 (d. d, 1H, J=4.0 and 2.0 Hz), 5.67 (br. s, 1H), and 7.1-7.3 (m, 10H). Found: C 77.25, H 6.05, N 10.65. $C_{17}H_{16}N_2O$ requires C 77.24, H 6.10, N 10.59%.

3,4-Dihydro-4-methyl-1,6-diphenyl-2(1H)-pyrimidinethione (170)

mp 162 °C (decomp., from ethyl acetate); IR: 3200, 1680, 1530, 1205, 760, and 690; PMR: 1.42 (d, 3H, J=6.0 Hz), 4.1-4.6 (m, 1H), 5.0-5.2 (d. d, 1H, J=4.0 and 2.0 Hz), 7.1-7.3 (m, 10H), and 8.0 (br. s, 1H). Found: C 72.75, H 5.7, N 9.9. $C_{17}H_{16}N_2S$ requires C 72.82, H 5.75, N 9.99%.

Also using Method D, 32 gave compounds 159 and 160, and 36 gave compounds 164 and 165.

Method E To a solution of 2(1H)-pyrimidinone (2 mmol) in methanol (20 ml) was added $NaBH_4$ (2 mmol), and the mixture was stirred for 3 hr at room temperature. Compound 55 gave compound 168 and 3,6-dihydro-4-methyl-1,6-diphenyl-2(1H)-pyrimidinone (169)[207]

mp 182-186 °C (from ethyl acetate); PMR: 1.77 (s, 3H), 4.6-4.8 (m, 1H), 5.0-5.3 (m, 1H), and 7.0-7.3 (m, 10H). Found [for a mixture of 168 and 169]: C 77.15, H 6.1, N 10.65. $C_{17}H_{16}N_2O$ requires C 77.25, H 6.10, N 10.59%.

Compound 59 gave compound 170 and 3,6-dihydro-4-methyl-1,6-diphenyl-2(1H)-pyrimidinethione (171)[207]

mp 207-212 °C (from ethyl acetate); PMR: 1.73 (s, 3H), 3.8-4.3 (m, 1H), 4.9-5.2 (m, 1H), and 6.8-7.3 (m, 10H). Found [for a mixture of 170 and 171]: C 73.15, H 5.75, N 10.1. $C_{17}H_{16}N_2S$ requires C 72.82, H 5.75, N 9.99%.

Also using Method E compound 54 gave compound 167.

Method F $NaBH_4$ (10 mmol) was added slowly to a solution

of 2(1H)-pyrimidinone (1 mmol) in acetic acid (8 ml) and the mixture was stirred for 1 hr at room temperature. The reaction mixture was neutralized cautiously with aqueous sodium hydroxide, on an ice-water bath, and then extracted with dichloromethane and dried over anhydrous magnesium sulfate.

Tetrahydro-1-(o-tolyl)-2(1H)-pyrimidinone (172)

mp 193-194 °C (from ethyl acetate); IR: 3220, 3060, 1650, 1500, 755, and 720; PMR: 1.8-2.2 (m, 2H), 2.33 (s, 3H), 3.2-3.6 (m, 4H), 6.28 (br. s, 1H), and 7.1-7.3 (m, 4H). Found: C 69.7, H 7.45, N 14.75. $C_{11}H_{14}N_2O$ requires C 69.44, H 7.41, N 14.72%.

Tetrahydro-1,6-dimethyl-4-phenyl-2(1H)-pyrimidinone (173)

mp 124-125 °C (from benzene-hexane); IR: 3210, 3060, 2960, 1650, 745, and 690; PMR: 1.18 (d, 3H, J=6.0 Hz), 1.6-2.4 (m, 2H), 2.93 (s, 3H), 3.2-3.8 (m, 1H), 4.3-4.7 (d. d, 1H, J=10.5 and 4.0 Hz), 5.10 (br. s, 1H), and 7.2-7.4 (m, 5H). Found: C 70.4, H 7.85, N 13.6. $C_{12}H_{16}N_2O$ requires C 70.55, H 7.89, N 13.17%.

Tetrahydro-1-methyl-4,6-diphenyl-2(1H)-pyrimidinone (174)

mp 219 °C (from benzene); IR: 3200, 3070, 2960, 1640, 760, and 700; PMR: 1.9-2.4 (m, 2H), 2.73 (s, 3H), 4.3-4.8 (m, 2H), 4.97 (br. s, 1H), and 7.3-7.5 (m, 10H). Found: C 76.45, H 6.7, N 10.25. $C_{17}H_{18}N_2O$ requires C 76.66, H 6.81, N 10.51%.

Tetrahydro-4,6-dimethyl-1-(p-tolyl)-2(1H)-pyrimidinone (175)

mp 220-221 °C (from benzene); IR: 3210, 2960, 1660, 1600, and 800; PMR: 0.93 (d, 3H, J=6.0 Hz), 1.20 (d, 3H, J=6.0 Hz), 1.7-2.1 (m, 2H), 2.35 (s, 3H), 3.4-4.1 (m, 2H), 4.8 (br. s, 1H), and 7.0-7.3 (m, 4H). Found: C 71.5, H 8.25, N 12.8. $C_{13}H_{18}N_2O$ requires C 71.52, H 8.31, N 12.83%.

Tetrahydro-1-(p-methoxy)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (176)

mp 218-219 °C (from benzene); IR: 3230, 2970, 1660, 820, and 740; PMR: 0.93 (d, 3H, J=6.0 Hz), 1.18 (d, 3H, J=6.0 Hz), 1.6-2.1 (m, 2H), 3.79 (s, 3H), 3.5-4.2 (m, 2H), and 6.8-7.4 (m, 4H). Found: C 66.70 H 7.75 N 11.95. $C_{13}H_{18}N_2O_2$ requires C 66.64, H 7.74, N 11.95%.

Tetrahydro-1-(p-chloro)phenyl-4,6-dimethyl-2(1H)-pyrimidinone (177)

mp 240-241 °C (from benzene); IR: 3240, 2990, 1660, 820, and 750; PMR: 0.97 (d, 3H, J=6.0 Hz), 1.18 (d, 3H, J=6.0 Hz), 1.4-2.1 (m, 2H), 3.4-4.1 (m, 2H), 5.0 (br. s, 1H), and 7.0-7.5 (m, 4H). Found: C 60.4, H 6.3, N 11.75. $C_{12}H_{15}ClN_2O$ requires C 60.37, H 6.33, N 11.73%.

Tetrahydro-6-methyl-1,4-diphenyl-2(1H)-pyrimidinone (178)

mp 189 °C (from benzene-hexane); IR: 3220, 3060, 1650, 1430, 750, and 690; PMR: 0.95 (d, 3H, J=6.0 Hz), 1.7-2.5 (m, 2H), 3.8-4.3 (m, 1H), 4.5-4.8 (d. d, 1H, J=10.5 and 4.0 Hz), 5.17 (br. s, 1H), and 7.2-7.6 (m, 10H). Found: C 76.45, H 6.75, N 10.5. $C_{17}H_{18}N_2O$ requires C 76.66, H 6.81, N 10.51%

3,4-Dihydro-4,6-diphenyl-1-(p-tolyl)-2(1H)-pyrimidinone (179)

mp 154-155 °C (from ethyl acetate-hexane); IR: 3230, 3080, 1690, 750, and 700; PMR: 2.13 (s, 3H), 5.0-5.3 (m, 2H), 6.13 (br. s, 1H), and 6.9-7.5 (m, 14H). Found: C 80.95, H 5.85, N 8.25. $C_{23}H_{20}N_2O$ requires C 81.14, H 5.92, N 8.22%.

Tetrahydro-4,6-diphenyl-1-(p-tolyl)-2(1H)-pyrimidinone (180)

mp 233 °C (from ethyl acetate); IR: 3240, 1660, 1430, 765, and 750; PMR: 2.1-2.7 (m, 2H), 2.16 (s, 3H), 4.7-5.3 (m, 2H), and 6.9-7.5 (m, 14H). Found: 80.45, H 6.35, N 8.1. $C_{23}H_{22}N_2O$ requires C 80.67, H 6.47, N 8.18%.

3,4-Dihydro-1-phenyl-2(1H)-pyrimidinone (181)

mp 170-171 °C (from ethyl acetate); IR: 3240, 1685, 1660, 1290, 1140, 760, and 690; PMR: 4.0-4.3 (m, 2H), 4.7-5.1 (m, 1H), 6.07 (br. s, 1H), 6.2-6.5 (d. t, 1H, J=8.0 and 1.5 Hz), and 7.1-7.4 (m, 5H). Found: C 68.7, H 5.75, N 16.0. $C_{10}H_{10}N_2O$ requires C 68.94, H 5.78, N 16.08%.

Tetrahydro-1-phenyl-2(1H)-pyrimidinone (182)

mp 205 °C (from ethyl acetate); IR: 3220, 3060, 1650, 760, and 695; PMR: 1.8-2.3 (m, 2H), 3.2-3.5 (m, 2H), 3.5-3.9 (m, 2H), 6.20 (br. s, 1H), and 7.2-7.6 (m, 5H). Found: C 68.15, H 6.8, N 15.85. $C_{10}H_{12}N_2O$ requires C 68.15, H 6.86, N 15.89%.

3,4-Dihydro-1-(p-methoxy)phenyl-2(1H)-pyrimidinone (183)

mp 178-180 °C (from ethyl acetate-hexane); IR: 3240, 2960, 1695, 1670, 1440, 1245, and 825; PMR: 3.82 (s, 3H), 4.1-4.3 (m, 2H), 4.7-5.1 (m, 1H), 5.40 (br. s, 1H), 6.1-6.4

(d. t, 1H, J=8.0 and 1.5 Hz), 6.8-7.1 (m, 2H), and 7.1-7.4 (m, 2H). Found: C 64.5, H 5.9, N 13.65. $C_{11}H_{12}N_2O$ requires C 64.69, H 5.92, N 13.71%.

3,4-Dihydro-1-phenyl-2(1H)-pyrimidinethione (185)

mp 165 °C (decomp., from ethyl acetate); IR: 3210, 1675, 1555, 1270, and 695; PMR: 4.0-4.2 (m, 2H), 4.9-5.3 (m, 1H), 6.0-6.3 (d. t, 1H, J=8.0 and 1.5 Hz), 7.2-7.5 (m, 5H), and 7.76 (br. s, 1H). Found: C 63.25, H 5.2, N 14.55. $C_{10}H_{10}N_2S$ requires C 63.12, H 5.29, N 14.72%.

Tetrahydro-1-phenyl-2(1H)-pyrimidinethione (186)

mp 211-212 °C (from ethyl acetate); IR: 3200, 1540, 1500, 1195, 770, and 700; PMR: 1.9-2.3 (m, 2H), 3.2-3.8 (m, 4H), 7.2-7.4 (m, 5H), and 7.90 (br. s, 1H). Found: C 62.3, H 6.25, N 15.0. $C_{10}H_{12}N_2S$ requires C 62.46, H 6.29, N 14.56%.

Tetrahydro-4-methyl-1,6-diphenyl-2(1H)-pyrimidinethione (187)

mp 204-205 °C (from ethyl acetate); IR: 3200, 3030, 1600, 1260, 760, and 690; PMR: 1.23 (d, 3H, J=6.0 Hz), 2.0-2.5 (m, 2H), 3.6-4.1 (m, 1H), 4.8-5.1 (d. d, 1H, J=9.5 and 6.0 Hz), and 7.0-7.5 (m, 10H). Found: C 72.45, H 6.4, N 9.9. $C_{17}H_{18}N_2S$ requires C 72.30, H 6.42, N 9.91%.

## Desulfuration with Raney Nickel

The mixture of 2(1H)-pyrimidinethione (5 mmol) and Raney nickel (Ni-Al 50% alloy, 4 g) in methanol (20 ml) was

stirred at room temperature for 3 hr under an argon atmosphere. After removal of the catalyst by filtration, the filtrate was diluted with water and extracted with dichloromethane, then dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with hexane-acetone-diethylamine (13:6:1).

1,2-Dihydro-4,6-dimethyl-1-phenylpyrimidine (90)

mp (as picrate) 127-128 °C; IR: 1610, 1590, 1530, and 855; UV: 343; PMR: 1.83 (d, 3H, J=0.6 Hz), 2.20 (s, 3H), 4.98 (s, 2H), 5.37 (q, 1H, J=0.6 Hz), and 7.1-7.5 (m, 5H). Found (as picrate): 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%.

1,2-Dihydro-1,4-dimethyl-6-phenylpyrimidine (191)

mp (as picrate) 116 °C; UV: 355 (3.59); PMR: 2.03 (s, 3H), 2.72 (s, 3H), 4.70 (s, 2H), 5.47 (s, 1H), and 7.2-7.6 (m, 5H). Found (as picrate): C 52.32, H 4.08, N 16.85. $C_{18}H_{17}N_5O_7$ requires C 52.05, H 4.12, N 16.86%.

1,2-Dihydro-4,6-dimethyl-1-(p-tolyl)pyrimidine (192)

mp (as picrate) 134-135 °C; IR: 1620, 1515, 1425, 1265, 1215, 905, and 730; UV: 343 (3.71); PMR: 1.81 (d, 3H, J=0.6 Hz), 2.01 (s, 3H), 2.33 (s, 3H), 4.93 (s, 2H), 5.43 (q, 1H, J=0.6 Hz), and 6.9-7.4 (m, 4H). Found (as picrate): C 53.27, H 4.38, N 16.28. $C_{19}H_{19}N_5O_7$ requires C 53.14, H 4.46, N 16.31%.

1,2-Dihydro-4,6-dimethyl-1-(p-methoxy)phenylpyrimidine (193)

mp (as picrate) 119-120 °C; IR: 1615, 1510, 1245, 1135, 1035, 905, and 835; UV: 343 (3.68); PMR: 1.76 (d, 3H, J=0.6 Hz),

1.98 (s, 3H), 3.77 (s, 3H), 4.87 (s, 2H), 5.27 (q, 1H, J= 0.6 Hz), and 6.7-7.2 (m, 4H). Found: C 51.36, H 4.25, N 15.80. $C_{19}H_{19}N_5O_8$ requires C 51.23, H 4.30, N 15.72%.

## Photochemical Reaction

A solution of 2(1H)-pyrimidinone (1 mmol) in solvent (45 ml) was irradiated in a Pyrex vessel under an argon atmosphere with a high-pressure mercury lamp for 10-50 hr at room temperature. After removal of the solvent, the residue was chromatographed on a silica gel column. Elution with benzene-ethyl acetate (4:1 or 2:1) afforded the photoproduct and then elution with ethyl acetate gave the unreacted 2(1H)-pyrimidinone.

3-phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo[2.2.0]hex-5-ene (195)

(from benzene-hexane); IR: 1760, 1640, 1600, 1500, 1380, and 750; UV: 270 (4.20) and 280 (4.10); PMR: 1.83 (s, 3H), 2.08 (d, 3H, J=1.5 Hz), 6.00 (q, 1H, J=1.5 Hz), 6.7-7.4 (m, 5H); m/e 200 ($M^+$), 185, 172, 119, 81, 80, 77, and 76. Found: C 72.15, H 6.1, N 13.85. $C_{12}H_{12}N_2O$ requires C 71.95, H 6.05, N 14.0%.

3,4,6-Trimethyl-2-oxo-1,3-diazabicyclo[2.2.0]hex-5-ene (199)

IR: 1760, 1635, and 1380; PMR: 1.58 (s, 3H), 2.00 (d, 3H, J=1.7 Hz), 2.75 (s, 3H), and 5.80 (q, 1H, J=1.7 Hz); m/e 138 ($M^+$), 123, 110, 97, 81, and 56. Found: C 60.6, H 7.15,

N 20.55. $C_7H_{10}N_2O$ requires C 60.85, H 7.3, N 20.25%.

3-(o-Tolyl)-4,6-dimethyl-2-oxo-1,3-diazabicyclo[2.2.0]hex-5-ene (200)

(from benzene-hexane); IR: 1770, 1640, 1605, 1500, 1380, and 750; UV: 229 (4.0) and 267 (3.91); PMR: 1.58 (s, 3H), 2.04 (d, 3H, J=1.5 Hz), 2.31 (s, 3H), 5.98 (q, 1H, J=1.5 Hz), and 6.9-7.1 (m, 4H); m/e 214 ($M^+$), 199, 186, 185, 90, 80, 77, and 76. Found: C 72.85, H 6.6, N 12.85. $C_{13}H_{14}N_2O$ requires C 72.85, H 6.6, N 13.05%.

3-(o-Methoxy)phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo-[2.2.0]hex-5-ene (201)

IR: 1775, 1640, 1590, 1505, 1360, and 760; PMR: 1.74 (s, 3H), 2.11 (d, 3H, J=1.5 Hz), 3.87 (s, 3H), 6.16 (q, 1H, J=1.5 Hz), 6.8-7.3 (m, 2H), 7.3-7.5 (m, 1H), and 7.6-7.9 (m, 1H). Found: C 73.55, H 6.95, N 12.25. $C_{13}H_{14}N_2O_2$ requires C 73.65, H 7.05, N 12.25%.

3-(o-Ethyl)phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo-[2.2.0]hex-5-ene (202)

IR: 1780, 1640, 1600, 1495, 1365, and 755; PMR: 1.20 (t, 3H, J=7.0 Hz), 1.61 (s, 3H), 2.07 (d, 3H, J=1.7 Hz), 2.70 (q, 2H, J=7.0 Hz), 6.03 (q, 1H, J=1.7 Hz), and 6.8-7.2 (m, 4H); m/e 228 ($M^+$), 213, 200, 199, 198, and 144. Found: C 73.55, H 6.95, N 12.25. $C_{14}H_{16}N_2O$ requires C 73.65, H 7.05, N 12.25%.

3-(o-Ethoxy)phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo-[2.2.0]hex-5-ene (203)

IR: 1770, 1640, 1595, 1380, and 745; PMR: 1.41 (t, 3H), 1.70 (s, 3H), 2.04 (d, 3H, J=1.5 Hz), 3.94 (q, 2H), 5.87 (q, 1H, J=1.5 Hz), 6.5-7.1 (m, 3H), and 7.2-7.5 (m, 1H); m/e 244 ($M^+$), 229, 216, 214, and 199. Found: C 68.7, H 6.5, N 11.55. $C_{14}H_{16}N_2O_2$ requires C 68.85, H 6.6, N 11.45%.

3-(o-Chloro)phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo-[2.2.0]hex-5-ene (204)

IR: 1775, 1640, 1585, 1485, 1365, and 755; PMR: 1.72 (s, 3H), 2.09 (d, 3H, J=1.5 Hz), 6.04 (q, 1H, J=1.5 Hz), and 6.9-7.6 (m, 4H). Found: C 61.25, H 4.75, N 12.2. $C_{12}H_{11}ClN_2O$ requires C 61.4, H 4.75, N 11.95%.

3-(p-Tolyl)-4,6-dimethyl-2-oxo-1,3-diazabicyclo[2.2.0]hex-5-ene (205)

(from benzene-hexane); IR: 1765, 1638, 1610, 1510, 1385, 810, and 765; UV: 243 (4.79), 275 (4.17), and 285 (4.02); PMR: 1.83 (s, 3H), 2.10 (d, 3H, J=1.5 Hz), 2.32 (s, 3H), 6.15 (q, 1H, J=1.5 Hz), and 7.20 (m, 4H); m/e 214 ($M^+$), 199, 186, 90, 80, 77, and 76. Found: C 73.0, H 6.6, N 13.05. $C_{13}H_{14}N_2O$ requires C 72.85, H 6.6, N 13.05%.

3-(p-Methoxy)phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo-[2.2.0]hex-5-ene (206)

(from benzene-hexane); IR: 1770, 1640, 1580, 1510, 1395, 840, and 760; PMR: 1.74 (s, 3H), 2.02 (d, 3H, J=1.5 Hz), 3.64 (s, 3H), 5.88 (q, 1H, J=1.5 Hz), 6.64 (d, 2H, J=6.4 Hz), and 6.94 (d, 2H, J=6.4 Hz). Found: C 72.45, H 6.6, N 13.35. $C_{13}H_{14}N_2O_2$ requires C 72.85, H 6.6, N 13.05%.

3-(β-Naphthyl)-4,6-dimethyl-2-oxo-1,3-diazabicyclo[2.2.0]hex-5-ene (207)

IR: 3050, 1780, 1643, 1515, 1380, 1360, 800, 780, and 680; PMR: 1.69 (s, 3H), 2.15 (d, 3H, J=1.5 Hz), 6.18 (q, 1H, J= 1.5 Hz), and 7.0-8.2 (m, 7H). Found: C 76.65, H 5.6, N 11.0. $C_{16}H_{14}N_2O$ requires C, 76.75, H 5.65, N 11.2%.

3,6-Dimethyl-4-phenyl-2-oxo-1,3-diazabicyclo[2.2.0]hex-5-ene (208)

(from benzene-hexane); IR: 1775, 1650, 1390, 1380, 765, and 700; PMR: 2.08 (d, 3H, J=1.4 Hz), 2.75 (s, 3H), 6.18 (q, 1H, J=1.4 Hz), and 7.2-7.3 (m, 5H). Found: C 72.0, H 5.85, N 13.65. $C_{12}H_{12}N_2O$ requires C 71.95, H 6.05, N 14.0%.

Hydrogenation of Compound (195) A solution of compound 195 (100 mg) in methanol (20 ml) was hydrogenated over palladium-charcoal (50 mg). The usual work-up gave 3-phenyl-4,6-dimethyl-2-oxo-1,3-diazabicyclo[2.2.0]hexane (196).

(60 mg); mp 115-116 °C (from benzene-hexane); IR: 1765, 1600, 1500, 1380, and 690; PMR: 1.45 (d, 3H, J=7.2 Hz), 1.73 (s, 3H), 2.56 (d. d, 1H, J=7.2 and 12.8 Hz), and 6.9-7.6 (m,5H). Found: C 71.05, H 7.0, N 13.55. $C_{12}H_{14}N_2O$ requires C 71.25, H 7.0, N 13.6%.

Reaction of Compound (195) with Potassium Methoxide To a solution of potassium (20 mg) in methanol (5 ml) was added

dropwise a solution of compound 195 (100 mg) in methanol (10 ml) with stirring. The mixture was stirred for 3 hr at room temperature, poured into an ice-water, and then extracted with dichloromethane. The extract was washed with 10% hydrochloric acid and water, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residual oil was chromatographed on silica gel with benzene.

Methyl N-Phenylcarbamate (197)

(70 mg); bp 150 °C at 4 mmHg (Kugelrohr temperature); IR: 3300, 1735, 1700, 760, and 695; PMR: 3.75 (s, 3H), 6.8 (br. s, 1H, $D_2O$ exchangeable), and 7.0-7.5 (m, 5H). Found: C 63.55, H 5.95, N 9.15. $C_8H_9NO_2$ requires C 63.55, H 6.0, N 9.25%.

Treatment of Compound (195) with Hydrochloric Acid To a solution of compound 195 (100 mg) in methanol (10 ml) was added a few drops of concentrated hydrochloric acid. The mixture was stirred for 20 hr at room temperature, poured into water, and extracted with dichloromethane. The extract was washed with 10% sodium hydrogen carbonate solution and water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) quantitatively.

Quantum Yield Determinations Benzophenone-benzhydrol actinometry was used for quantum yield determination. The

300-nm line of a Ravonet photochemical reactor was used as an irradiation source. Sample (0.1 M solution) in Pyrex tubes were degassed to ca. $10^{-3}$ mmHg in three freeze-thaw cycles and sealed. The samples were irradiated individually in succession. Photolyses were carried out to 30-50% conversion. The degree of reaction was determined by GLC.

## Ring Opening Reaction

Reaction with Hydroxylamine To a solution of 3,6-dihydro-2(1H)-pyrimidinone (3 mmol) in the presence of sodium hydroxide (6.6 mmol) in absolute ethanol (40 ml) was added hydroxylamine hydrochloride (3.3 mmol), and the mixture was refluxed for 34 hr. The reaction mixture was diluted with water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with benzene-ethyl acetate (2:1) or (4:1), followed by vacuum distillation.

2-Anilino-2-methyl-pentan-4-one oxime (221)

IR: 2800-3500, 1605, 1495, 740, and 690; PMR: 1.33 (s, 6H), 2.52 (s, 2H), 6.6-7.0 (m, 3H), and 7.0-7.4 (m, 2H). Found: C 68.96, H 8.75, N 13.66. $C_{12}H_{18}N_2O$ requires C 68.86, H 8.79, N 13.57%.

2-Anilino-pentan-4-one oxime (222)

IR: 2800-3500, 1600, and 740; PMR: 1.22 (d, 3H, J=6.0 Hz), 1.90 (s, 3H), 3.5-4.1 (m, 2H), 2.3-2.6 (d. d, 2H, J=6.0 and

4.0 Hz), 6.5-6.9 (m, 3H), and 7.0-7.4 (m, 2H). Found: C 68.55, H 8.29, N 14.67. $C_{11}H_{16}N_2O$ requires C 68.71, H 8.38, N 14.57%.

2-(p-Chloro)anilino-pentan-4-one oxime (224)

IR: 2800-3500, 1600, and 810; PMR: 1.24 (d, 3H, J=6.0 Hz), 1.83 (s, 3H), 3.5-4.0 (m, 2H), 2.2-2.5 (d. d, 2H, J=6.0 and 4.0 Hz), 6.4-6.7 (m, 2H), and 7.0-7.4 (m, 2H). Found: C 57.96, H 6.64, N 12.22. $C_{11}H_{15}ClN_2O$ requires C 58.27, H 6.66, N 12.35%.

2-Anilino-4-phenyl-butan-4-one oxime (225)

IR: 2800-3500, 1600, 1510, 760, and 695; PMR: 1.20 (d, 3H, J=6.0 Hz), 3.6-4.1 (m, 2H), 2.6-3.0 (d. d, 2H, 1H, J=13.0 and 7.0 Hz), 3.1-3.5 (d. d, 1H, J=13.0 and 6.5 Hz), 6.4-6.8 (m, 3H), and 7.0-7.8 (m, 7H). Found: C 75.23, H 7.08, N 10.97. $C_{16}H_{18}N_2O$ requires C 75.56, H 7.13, N 11.01%.

2-Anilino-butan-4-one oxime (226)

IR: 2800-3500, 1600, 1500, 745, and 690; PMR: 1.22 (d, 3H, J=6.0 Hz), 3.4-3.9 (m, 2H), 7.48 (t, 1H, J=6.0 Hz), 2.38 (t, 2H, J=6.0 Hz), 6.5-6.9 (m, 3H), and 7.0-7.3 (m, 2H). Found: C 66.98, H 7.98, N 15.42. $C_{10}H_{14}N_2O$ requires C 67.36, H 7.81, N 15.72%.

Alternative Preparation of Compound (221) The mixture of mesityl oxide (10 mmol) and aniline (40 mmol) was heated at 200 °C for 5 hr in a sealed tube. To the mixture in absolute ethanol (80 ml) was added hydroxylamine hydrochloride

(10 mmol) and anhydrous potassium carbonate (5 mmol). The reaction mixture was refluxed for 12 hr and was treated according to the procedure described above, yield 8%.

## Oxidation

Oxidation with Chloranil Chloranil (1.2 mmol) was added to the solution of tetrahydro-2(1H)-pyrimidinone (1 mmol) in dichloromethane (20 ml). The mixture was stirred for an hour at room temperature and the yield was determined by LPC. The results were listed in Table 33.

## Reductive Ring Opening Reaction

Tetrahydro-4,6,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (236)

3,6-Dihydro-4,6,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (137) was reduced with $NaBH_4$ in acetic acid according to the method[159] previously reported.

mp 182-182.5 °C (from benzene-hexane); yield 81%; IR: 3300, 1660, 1340, 1080, 760, and 700; PMR: 0.98 (s, 3H), 1.14 (d, 3H, J=6.0 Hz), 1.30 (s, 3H), 1.5-1.8 (m, 2H), 3.4-3.9 (m, 1H), 5.66 (br. s, 1H), and 7.0-7.5 (m, 5H). Found: C 71.74, H 8.33, N 12.78. $C_{13}H_{18}N_2O$ requires C 71.52, H 8.31, N 12.83%.

Tetrahydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (238)

3,4-Dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone

(138) was worked up according to the manner described above. mp 144-144.5 °C (from ethyl acetate-hexane); yield 82%; IR: 3280, 1650, 1600, 1200, 1070, and 690; PMR: 0.96 (d, 3H, J= 6.0 Hz), 1.23 (s, 3H), 1.32 (s, 3H), 1.5-1.9 (m, 2H), 3.8-4.2 (m, 1H), 5.23 (br. s, 1H), and 7.1-7.4 (m, 5H). Found: C 71.74, H 8.32, N 12.92. $C_{13}H_{18}N_2O$ requires C 71.52, H 8.31, N 12.83%.

Tetrahydro-3,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (240)

Compound 161 (4 mmol) was stirred for an hour in dry THF (20 ml) in the presence of sodium hydride (8 mmol), and then methyl iodide (16 mmol) in dry THF (10 ml) was added dropwise to the mixture. After refluxing for another an hour, the reaction mixture was washed with water, then the organic layer was dried over anhydrous magnesium sulfate.
mp 72-72.5 °C (from hexane); yield 84%; IR: 1640, 1590, 1220, 760, and 690; PMR: 0.97 (d, 3H, J=6.0 Hz), 1.31 (d, 3H, J= 6.0 Hz), 1.5-2.4 (m, 2H), 2.95 (s, 3H), 3.3-4.1 (m, 2H), and 7.1-7.4 (m, 5H). Found: C 71.22, H 8.33, N 12.94. $C_{13}H_{18}N_2O$ requires C 71.52, H 8.31, N 12.83%.

Reaction with $LiAlH_4$ A solution of tetrahydro-2(1H)-pyrimidinone (2 mmol) in dry benzene (15 ml) was added to a well-stirred suspension of $LiAlH_4$ (20 mmol) in dry THF (15 ml). After refluxing for 20 hr, the reaction mixture was cooled, and the excess of $LiAlH_4$ was decomposed by slow addition of ethyl acetate and water. The precipitate

was filtered off and then the filtrate was extracted with dichloromethane. The crude product was purified by column chromatography on silica gel with chloroform-acetone-ethanol-triethylamine (100:40:8:10), followed by vacuum distillation.

2-Anilino-4-methylaminopentane (231)

IR: 3280, PMR: 1.05 (d, 3H, J=6.0 Hz), 1.15 (d, 3H, J=6.0 Hz), 1.3-1.9 (m, 2H), 2.34 (s, 3H), 2.5-3.0 (m, 1H), 2.94 (br. s, 1H), 3.4-3.9 (m, 1H), 6.5-6.9 (m, 3H), and 7.1-7.4 (m, 2H). Found: C 74.67, H 10.49, N 14.27. $C_{12}H_{20}N_2$ requires C 74.94, H 10.48, N 14.56%.

4-Methylamino-2-(p-toluidino)pentane (234)

IR: 3300; PMR: 1.12 (d, 3H, J=6.0 Hz), 1.15 (d, 3H, J=6.0 Hz), 1.4-2.0 (m, 2H), 2.23 (s, 3H), 2.43 (s, 3H), 2.4-3.0 (m, 1H), 3.13 (br. s, 1H), 3.4-4.0 (m, 1H), 6.5-6.8 (m, 2H), and 6.9-7.2 (m, 2H). Found: C 74.46, H 10.76, N 13.41. $C_{13}H_{22}N_2O \cdot 0.2H_2O$ requires C 74.42, H 10.68, N 13.35%.

2-(p-Methoxy)anilino-4-methylaminopentane (235)

IR: 3280; PMR: 1.07 (d, 3H, J=6.0 Hz), 1.17 (d, 3H, J=6.0 Hz), 1.3-1.8 (m, 2H), 2.40 (s, 3H), 2.57 (br. s, 2H), 2.5-3.0 (m, 1H), 3.4-3.8 (m, 1H), 3.74 (s, 3H), and 6.5-6.9 (m, 4H). Found: C 70.12, H 10.01, N 12.35. $C_{13}H_{22}N_2O$ requires C 70.22, H 9.97, N 12.60%.

2-Anilino-2-methyl-4-methylaminopentane (237)

IR: 3280; PMR: 1.05 (d, 3H, J=6.0 Hz), 1.30 (s, 6H), 1.4-2.0 (m, 2H), 2.39 (s, 3H), 2.5-3.3 (m, 3H), 6.5-6.9 (m, 3H),

and 7.0-7.3 (m, 2H). Found: C 75.55, H 10.81, N 13.67. $C_{13}H_{22}N_2$ requires C 75.67, H 10.74, N 13.57%.

4-Anilino-2-methyl-2-methylaminopentane (239)

IR: 3280; PMR: 1.10 (s, 6H), 1.17 (d, 3H, J=6.0 Hz), 1.4-2.0 (m, 2H), 2.34 (s, 3H), 3.2-4.0 (m, 3H), 6.5-6.9 (m, 3H), and 7.0-7.3 (m, 2H). Found: C 74.92, H 10.72, N 13.44. $C_{13}H_{22}N_2O \cdot 0.1H_2O$ requires C 75.07, H 10.68, N 13 47%.

Hexahydro-3,4,6-trimethyl-1-phenylpyrimidine (233)

Compound 240 was treated with $LiAlH_4$ according to the manner described above. The crude product was purified by column chromatography on silica gel with chloroform-acetone-ethanol (100:40:8), followed by vacuum distillation.
bp 36 °C/$10^{-4}$ mmHg; yield 60%; IR: 2940, 1590, 1365, 1255, 750, and 690; PMR: 0.95 (d, 3H, J=6.0 Hz), 1.13 (d, 3H, J= 6.0 Hz), 1.4-1.8 (m, 2H), 2.25 (s, 3H), 2.4-3.2 (m, 2H), 3.23 (d, 1H, J=10 Hz), 3.90 (d, 1H, J=10 Hz), and 7.0-7.4 (m, 5H). Found: C 75.86, H 9.91, N 13.67. $C_{13}H_{20}N_2O \cdot 0.1H_2O$ requires C 75.80, H 9.82, N 13.61%.

Compound 233 was also obtained by stirring the mixture of compound 231 (2 mmol) and 37% formaldehyde (6 mmol) in benzene (25 ml) for 3 hr at room temperature.

## Preparation and Decomposition

Reaction with Sodium Nitrite To a solution of tetrahydro-

2(1H)-pyrimidinone (1 mmol) in 6N hydrochloric acid (1 ml) was added slowly sodium nitrite (6 mmol) at room temperature. After stirring for an hour, the mixture was neutralized with 10% sodium hydroxide, and extracted with dichloromethane. The crude product was chromatographed on silica gel with chloroform-ethyl acetate (20:1), and recrystallized from an appropriate solvent.

Tetrahydro-4,6-dimethyl-3-nitroso-1-phenyl-2(1H)-pyrimidinone (243)

(from benzene-hexane); IR: 1690, 1490, and 740; PMR: 1.08 (d, 3H, J=7.0 Hz), 1.25 (d, 3H, J=7.0 Hz), 1.8-2.5 (m, 2H), 3.7-4.2 (m, 1H), 4.3-4.8 (m, 1H), and 7.1-7.4 (m, 5H); CMR: 19.3 (q), 21.1 (q), 36.0 (t), 47.2 (d), 52.2 (d), 128.0 (d), 128.5 (d), 129.3 (d), 139.3 (s), and 152.1 (s). Found: C 61.87, H 6.43, N 18.07. $C_{12}H_{15}N_3O_2$ requires C 61.78, H 6.48, N 18.02%.

Tetrahydro-1-methyl-3-nitroso-4,6-diphenyl-2(1H)-pyrimidinone (244)

(from ethyl acetate); Found: C 69.15, H 5.76, N 14.26. $C_{17}H_{17}N_3O_2$ requires C 69.13, H 5.80, N 14.22%.

Tetrahydro-4,6-dimethyl-3-nitroso-1-(p-tolyl)-2(1H)-pyrimidinone (245)

(from ethyl acetate-hexane); IR: 1690, 1420, 1120, 1000, 805, and 730; PMR: 1.07 (d, 3H, J=7.0 Hz), 1.23 (d, 3H, J=7.0 Hz), 1.7-2.4 (m, 2H), 2.33 (s, 3H), 3.7-4.1 (m, 1H), 4.4-4.8 (m, 1H), and 7.1-7.3 (m, 4H).

Tetrahydro-4,6-dimethyl-1-(p-methoxy)phenyl-3-nitroso-2(1H)-pyrimidinone (246)

(from ethyl acetate-hexane); IR: 1690, 1515, 1420, 1250, 1100, 815, and 735; PMR: 1.08 (d, 3H, J=7.0 Hz), 1.23 (d, 3H, J=7.0 Hz), 1.6-2.5 (m, 2H), 3.7-4.1 (m, 1H), 3.80 (s, 3H), 4.3-4.8 (m, 1H), and 6.9-7.4 (m, 4H). Found: C 59.31, H 6.50, N 15.97. $C_{13}H_{17}N_3O_3$ requires C 59.30, H 6.50, N 15.95%.

Tetrahydro-1-(p-chloro)phenyl-4,6-dimethyl-3-nitroso-2(1H)-pyrimidinone (247)

(from ethyl acetate-hexane); IR: 1490, 1220, 1095, 900, 810, 750, and 725; PMR: 1.17 (d, 3H, J=7.0 Hz), 1.25 (d, 3H, J=7.0 Hz), 1.7-2.6 (m, 2H), 3.8-4.1 (m, 1H), 4.4-4.8 (m, 1H), and 7.3-7.5 (m, 4H). Found: C 53.87, H 5.18, N 15.78. $C_{12}H_{14}ClN_3O_2$ requires C 53.83, H 5.27, N 15.69%.

Tetrahydro-1-(p-bromo)phenyl-4,6-dimethyl-3-nitrso-2(1H)-pyrimidinone (249)

(from ethyl acetate); IR: 1490, 1415, 1225, 1000, 905, 750, and 725; PMR: 1.13 (d, 3H, J=7.0 Hz), 1.25 (d, 3H, J=7.0 Hz), 1.7-2.6 (m, 2H), 3.7-4.1 (m, 1H), 4.4-4.8 (m, 1H), and 7.1-7.7 (m, 4H). Found: C 46.27, H 4.43, N 13.54. $C_{12}H_{14}BrN_3O_2$ requires C 46.17, H 4.52, N 13.46%.

Tetrahydro-3-nitroso-1-(p-tolyl)-2(1H)-pyrimidinone (251)

(from ethyl acetate). Found: 60.17, H 5.91, N 19.14. $C_{11}H_{13}N_3O_2$ requires C 60.26, H 5.97, N 19.16%.

Tetrahydro-6-methyl-3-nitroso-1-phenyl-2(1H)-pyrimidinone (253)

(from benzene-hexane); IR: 1680, 1400, 1095, and 740; PMR: 1.18 (d, 3H, J=7.0 Hz), 1.8-2.4 (m, 2H), 3.6-4.3 (m, 3H), and 7.2-7.6 (m, 5H). Found: C 60.35, H 5.96, N 19.30. $C_{11}H_{13}N_3O_2$ requires C 60.26, H 5.97, N 19.16%.

Decomposition with Potassium Hydroxide Tetrahydro-3-nitroso-2(1H)-pyrimidinone (2 mmol) in absolute methanol (10 ml) was added dropwise to the solution of potassium hydroxide (20 mmol) in absolute methanol (10 ml) with stirring at room temperature. After 4 hr, the reaction mixture was diluted with water, and extracted with dichloromethane. The crude product was first chromatographed on silica gel with benzene-ethyl acetate (10:1), followed by elution with chloroform-acetone-ethanol (100:5:1).

Methyl N-(1-penten-4-yl)phenylcarbamate (254)

bp 48 °C/$10^{-4}$ mmHg; IR: 1690, 1600, 1495, 1440, 1195, 1110, and 1060; PMR: 1.16 (d, 3H, J=6.0 Hz), 1.5-2.4 (m, 2H), 3.58 (s, 3H), 4.3-4.7 (m, 1H), 4.9-5.1 (m, 1H), 5.1-5.3 (m, 1H), 5.5-5.9 (m, 1H), and 7.0-7.5 (m, 5H). Found: C 71.02, H 7.79, N 6.49. $C_{13}H_{17}NO_2$ requires C 71.20, H 7.81, N 6.38%.

Methyl N-(2-methoxypent-4-yl)phenyl carbamate (255)

bp 59 °C/$10^{-4}$ mmHg; IR: 1705, 1595, 1495, 1440, 1325, 1085, and 695; PMR: 1.13 (d, 3H, J=6.0 Hz), 1.15 (d, 3H, J=6.0 Hz), 1.4-1.8 (m, 2H), 3.28 (s, 3H), 3.2-3.5 (m, 1H), 3.62 (s, 3H),

4.2-4.7 (m, 1H), and 7.0-7.5 (m, 5H). Found: C 66.60, H 8.39, N 5.68. $C_{14}H_{21}NO_3$ requires C 66.90, H 8.42, N 5.57%.

Tetrahydro-4,6-dimethyl-3-phenyl-1,3-oxazin-2-one (256)

mp 89-90 °C (from benzene-hexane); IR: 1645, 1400, 1270, 750, and 690; PMR: 1.15 (d, 3H, J=7.0 Hz), 1.43 (d, 3H, J=7.0 Hz), 1.7-2.2 (m, 2H), 3.8-4.2 (m, 1H), 4.4-4.8 (m, 1H), and 7.1-7.5 (m, 5H). Found: C 70.52, H 7.40, N 6.91. $C_{12}H_{15}NO_2$ requires C 70.22, H 7.36, N 6.82%.

Methyl N-(1-penten-4-yl)-p-tolylcarbamate (257)

IR: 1700, 1510, 1420, 1320, 1055, 815, and 765; PMR: 1.08 (d, 3H, J=6.0 Hz), 1.5-2.4 (m, 2H), 2.32 (s, 3H), 3.58 (s, 3H), 4.2-4.7 (m, 1H), 4.8-5.0 (m, 1H), 5.1-5.3 (m, 1H), 5.4-5.8 (m, 1H), and 7.0-7.3 (m, 4H).

Methyl N-(2-methoxypent-4-yl)-p-tolylcarbamate (258)

IR: 1700, 1510, 1440, 1320, 1080, 815, and 765; PMR: 1.15 (d, 3H, J=6.0 Hz), 1.16 (d, 3H, J=6.0 Hz), 1.4-2.0 (m, 2H), 2.33 (s, 3H), 3.28 (s, 3H), 3.2-3.5 (m, 1H), 3.60 (s, 3H), 4.3-4.8 (m, 1H), and 7.0-7.3 (m, 4H).

Tetrahydro-4,6-dimethyl-3-(p-tolyl)-1,3-oxazin-2-one (259)

IR: 1690, 1510, 1410, and 1275; PMR: 1.13 (d, 3H, J=7.0 Hz), 1.40 (d, 3H, J=7.0 Hz), 1.6-2.2 (m, 2H), 2.32 (s, 3H), 3.8-4.2 (m, 1H), 4.3-4.9 (m, 1H), and 7.1-7.3 (m, 4H).

## S-Methylation

Reaction with Methyl Iodide Dihydro-2(1H)-pyrimidine-

thione (6 mmol) was stirred for an hour in distilled benzene (30 ml) in the presence of sodium hydride (12 mmol), and then methyl iodide (24 mmol) in distilled benzene (20 ml) was added dropwise to the mixture. After refluxing for 4 hr, the reaction mixture was washed with water, and then the organic layer was dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with chloroform-benzene-ethyl acetate (4:4:1).

1,4-Dihydro-4,6-dimethyl-2-methylthio-1-phenylpyrimidine (260)

IR: 1680, 1605, 1590, 1490, 1120, 1180, and 690; PMR: 1.30 (d, 3H, J=6.0 Hz), 1.45 (d. d, 3H, J=1.2 Hz), 2.23 (s, 3H), 4.2-4.4 (m, 1H), 4.5-4.7 (m, 1H), and 7.2-7.5 (m, 5H); UV: 256.

1,4-Dihydro-4,4,6-trimethyl-2-methylthio-1-phenylpyrimidine (262)

mp 44-45 °C ; IR: 1670, 1580, 765, and 690; UV: 238 (3.78); PMR: 1.25 (s, 6H), 1.44 (d, 3H, J=1.2 Hz), 2.23 (s, 3H), 4.52 (q, 1H, J=1.2 Hz), and 7.2-7.4 (m, 5H). Found: C 68.30, H 7.38, N 11.34. $C_{14}H_{18}N_2S$ requires C 68.25, H 7.36, N 11.37%.

1,4-Dihydro-4-methyl-2-methylthio-1,6-diphenylpyrimidine (263)

IR: 1670, 1605, 1585, 1490, 1340, 1190, 760, and 690; PMR: 1.40 (d, 3H, J=6.0 Hz), 2.26 (s, 3H), 4.3-4.6 (d. q, J=6.0 and 3.6 Hz), 4.93 (d, 1H, J=3.6 Hz), and 7.0-7.3 (m, 10H).

1,4-Dihydro-4,4,6-trimethyl-2-methylthio-1-(p-tolyl)pyrimidine (265)

mp 97-98 °C; IR: 1660, 1585, 1250, 1180, and 820; PMR: 1.23 (s, 6H), 1.43 (d, 3H, J=1.2 Hz), 2.22 (s, 3H), 2.35 (s, 3H), 4.4-4.5 (q, 1H, J=1.2 Hz), and 7.1-7.3 (m, 4H). Found: C 69.22, H 7.74, N 10.72. $C_{15}H_{20}N_2S$ requires C 69.22, H 7.74, N 10.75%.

1,4-Dihydro-4,4,6-trimethyl-2-methylthio-1-(p-methoxy)phenylpyrimidine (267)

mp 53-55 °C; IR: 1670, 1590, 1500, 1240, 1175, and 820; PMR: 1.22 (s, 6H), 1.45 (d, 3H, J=1.2 Hz), 2.22 (s, 3H), 3.80 (s, 3H), 4.4-4.5 (q, 1H, J=1.2 Hz), and 6.8-7.3 (m, 4H). Found: C 65.28, H 7.32, N 10.12. $C_{15}H_{20}N_2OS$ requires C 65.18, H 7.29, N 10.31%.

1,6-Dihydro-4,6-dimethyl-2-methylthio-1-phenylpyrimidine (261)

IR: 1640, 1510, 1360, 1235, 760, and 700; PMR: 1.13 (d, 3H, J=6.0 Hz), 1.87 (d. d, 3H, J=1.2 Hz), 2.27 (s, 3H), 4.2-4.5 (m, 1H), 4.7-4.9 (d. q, 1H, J=4.0 and 1.2 Hz), and 7.3-7.5 (m, 5H); UV: 292.

1,6-Dihydro-4,6,6-trimethyl-2-methylthio-1-phenylpyrimidine (268)

mp 72-74 °C; IR: 1650, 1515, 1325, 765, and 695; UV: 286 (3.69); PMR: 1.15 (s, 6H), 1.87 (d, 3H, J=1.2 Hz), 2.27 (s, 3H), 4.6-4.7 (q, 1H, J=1.2 Hz), and 7.2-7.5 (m, 5H). Found: C 68.03, H 7.33, N 11.36. $C_{14}H_{18}N_2S$ requires C 68.25,

H 7.36, N 11.37%.

1,6-Dihydro-4,6-dimethyl-2-methylthio-1-(p-tolyl)pyrimidine (270)

IR: 1640, 1510, 1360, 1185, and 805; PMR: 1.12 (d, 3H, J= 6.0 Hz), 1.85 (d. d, 3H, J=1.2 Hz), 2.26 (s, 3H), 2.35 (s, 3H), 4.1-4.4 (m, 1H), 4.7-4.9 (d. q, 1H, J=4.0 and 1.2 Hz), and 7.1-7.3 (m, 4H).

## Desulfuration

Reaction with Raney Nickel The mixture of dihyro-2(1H)-pyrimidinethione (3 mmol) and Raney nickel (Ni-Al 50% alloy, 4 g) in methanol (20 ml) was warmed at 50 °C for an hour, and then refluxed for 2 hr. After removal of the catalyst by filtration, the filtrate was diluted with water and extracted with dichloromethane, then dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel with hexane-acetone-diethylamine (13:6:1).

1,4-Dihydro-4,4,6-trimethyl-1-phenylpyrimidine (271)

mp (as picrate) 145-147 °C; IR: 1680, 1590, 1490, and 760; UV: 257 (3.82); PMR: 1.25 (s, 6H), 1.55 (d, 3H, J=1.2 Hz), 4.47 (q, 1H, J=1.2 Hz), and 7.1-7.5 (m, 6H); CMR: 18.9 (q), 32.7 (q), 52.6 (s), 106.8 (d), 127.1 (d), 127.4 (d), 129.2 (d), 130.9 (s), and 144.4 (d). Found (as picrate): C 53.33, H 4.45, N 16.37. $C_{19}H_{19}N_5O_7$ requires C 53.14, H 4.46, N 16.31%.

1,4-Dihydro-4,6-dimethyl-1-phenylpyrimidine (272)

mp (as picrate) 155-156 °C; IR: 1680, 1620, 1590, 1490, 1280, 1160, 755, and 690; UV: 258 (3.77); PMR: 1.27 (d, 3H, J=6.0 Hz), 1.50 (d. d, 3H, J=1.2 Hz), 4.0-4.3 (m, 1H), 4.3-4.5 (m, 1H), and 7.0-7.5 (m, 6H). Found (as picrate): 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%.

1,4-Dihydro-4,6-dimethyl-1-(p-tolyl)pyrimidine (273)

mp (as picrate) 133-134 °C; IR: 1700, 1625, 1610, 1510, 1365, 1290, 1175, 910, and 815; PMR: 1.27 (d, 3H, J=6.0 Hz), 1.50 (d. d, 3H, J=1.2 Hz), 2.35 (s, 3H), 4.0-4.3 (m, 1H), 4.3-4.5 (m, 1H), and 6.9-7.3 (m, 4H). Found (as picrate): C 53.14, H 4.43, N 16.11. $C_{19}H_{19}N_5O_7$ requires C 53.14, H 4.46, N 16.31%.

1,4-Dihydro-4,6-dimethyl-1-(p-methoxy)phenylpyrimidine (274)

mp (as picrate) 114-115 °C; IR: 1690, 1620, 1510, 1285, 1245, 1165, 1105, 1030, 900, and 825; UV: 250 (3.60); PMR: 1.27 (d, 3H, J=6.0 Hz), 1.47 (d. d, 3H, J=1.2 Hz), 3.77 (s, 3H), 4.0-4.3 (m, 1H), 4.3-4.5 (m, 1H), and 6.7-7.2 (m, 5H). Found (as picrate): C 51.19, H 4.29, N 15.65. $C_{19}H_{19}N_5O_8$ requires C 51.23, H 4.30, N 15.72%.

1,4-Dihydro-4,4,6-trimethyl-1-(p-tolyl)pyrimidine (281)

mp (as picrate) 159-161 °C; IR: 1690, 1630, 1605, 1515, 1485, 1440, 1400, 1365, 1285, 1115, 1025, 910, 840, and 815; PMR: 1.25 (s, 6H), 1.52 (d, 3H, J=1.2 Hz), 2.33 (s, 3H), 4.3-4.5 (q, 1H, J=1.2 Hz), and 7.0-7.3 (m, 5H). Found (as picrate):

C 54.42, H 4.74, N 15.97. $C_{20}H_{21}N_5O_7$ requires C 54.17, H 4.77, N 15.79%.

1,4-Dihydro-4,4,6-trimethyl-1-(p-methoxy)phenylpyrimidine (282)

mp (as picrate) 119-120 °C; IR: 1685, 1610, 1505, 1335, 1240, 1030, 905, and 825; PMR: 1.24 (s, 6H), 1.56 (d, 3H, J=1.2 Hz), 3.80 (s, 3H), 4.35-4.45 (q, 1H, J=1.2 Hz), and 6.7-7.2 (m, 5H). Found (as picrate): C 52.41, H 4.55, N 15.35. $C_{20}H_{21}N_5O_8$ requires C 52.28, H 4.60, N 15.24%.

1,4-Dihydro-4,4,6-trimethyl-1-(p-chloro)phenylpyrimidine (283)

mp (as picrate) 120-121 °C; IR: 1680, 1610, 1595, 1485, 1335, 1180, 1020, and 820; PMR: 1.24 (s, 6H), 1.53 (d, 3H, J=1.2 Hz), 4.4-4.5 (q, 1H, J=1.2 Hz), and 6.9-7.5 (m, 5H). Found (as picrate): C 49.44, H 3.93, N 15.07. $C_{19}H_{18}ClN_5O_7$ requires C 49.20, H 3.91, N 15.09%.

1,4-Dihydro-4,4,6-trimethyl-1-(p-bromo)phenylpyrimidine (284)

IR: 1690, 1610, 1600, 1495, 1340, 1190, 1010, 915, 825, and 700; PMR: 1.27 (s, 6H), 1.57 (d, 3H, J=1.2 Hz), 4.4-4.5 (q, 1H, J=1.2 Hz), and 6.9-7.7 (m, 5H).

1,4-Dihydro-4,4,6-trimethyl-1-(m-tolyl)pyrimidine (285)

mp (as picrate) 170-171 °C; IR: 1685, 1605, 1585, 1490, 1335, 1305, 1260, 1185, 905, 845, and 700; UV: 257 (3.71); PMR: 1.24 (s, 6H), 1.57 (d, 3H, J=1.2 Hz), 2.37 (s, 3H), 4.4-4.5 (q, 1H, J=1.2 Hz), and 6.8-7.5 (m, 5H). Found (as picrate): C 53.93, H 4.74, N 15.57. $C_{20}H_{21}N_5O_7$ requires C 54.17,

H 4.77, N 15.79%.

1,4-Dihydro-1-benzyl-4,4,6-trimethylpyrimidine (286)

mp (as picrate) 105-106 °C; IR: 1685, 1615, 1495, 1450, 1440, 1355, 1315, 1215, 1170, 965, 820, and 690; PMR: 1.20 (s, 6H), 1.52 (d, 3H, J=1.2 Hz), 4.3-4.4 (q, 1H, J=1.2 Hz), 4.45 (s, 2H), 6.98 (s, 1H), and 7.2-7.4 (m, 5H). Found (as picrate): C 52.41, H 4.55, N 15.35. $C_{20}H_{21}N_5O_8$ requires C 52.28, H 4.60, N 15.24%.

1,6-Dihydro-4,6-dimethyl-1-phenylpyrimidine (289)

mp (as picrate) 131-132 °C; IR: 1650, 1560, 1490, 1360, 1270, and 1170; UV: 311; PMR: 1.23 (d, 3H, J=6.0 Hz), 1.87 (d. d, 3H, J=1.2 Hz), 4.5-4.8 (m, 1H), 4.8-5.0 (m, 1H), and 7.1-7.5 (m, 6H). Found (as picrate): C 52.26, H 4.10, N 16.73. $C_{18}H_{17}N_5O_7$ requires C 52.05, H 4.12, N 16.86%.

1,6-Dihydro-4,6-dimethyl-1-(p-tolyl)pyrimidine (290)

mp (as picrate) 155-156 °C; IR: 1670, 1570, 1515, 1375, 1280, 1180, 1125, and 915; UV: 310 (2.95); PMR: 1.20 (d, 3H, J= 6.0 Hz), 1.83 (d. d, 3H, J=1.2 Hz), 2.32 (s, 3H), 4.3-4.7 (m, 1H), 4.7-5.0 (m, 1H), and 6.9-7.3 (m, 5H). Found (as picrate): C 53.20, H 4.39, N 16.38. $C_{19}H_{19}N_5O_7$ requires C 53.14, H 4.46, N 16.31%.

1,6-Dihydro-4,6-dimethyl-1-(p-methoxy)phenypyrimidine (292)

mp (as picrate) 123-124 °C; IR: 1580, 1515, 1370, 1250, 1190, 1035, and 830; UV: 302 (3.57); PMR: 1.17 (d, 3H, J=6.0 Hz), 1.82 (d. d, 3H, J=1.2 Hz), 3.77 (s, 3H), 4.3-4.7 (m, 1H), 4.7-4.9 (m, 1H), and 6.7-7.3 (m, 5H). Found (as picrate):

C 51.30, H 4.30, N 15.70. $C_{19}H_{19}N_5O_8$ requires C 51.23, H 4.30, N 15.72%.

# VI SUMMARY

The chemistry of the restricted rotation around the carbon-nitrogen single bond has been scarcely explored. Also the nucleophilic reaction and synthetic utility of 1-substituted 2(1H)-pyrimidinones have been hardly investigated. Under these situations, the author believes that the elucidation of these points is quite important and will be extremely useful in organic chemistry. Therefore, in this thesis, the author describes the property and reaction of 1-aryl-2(1H)-pyrimidinones.

In Chapter II, the author investigated the preparation and physical property of 1-aryl-2(1H)-pyrimidinones. Recently, a number of papers on 2(1H)-pyrimidinones have been reported. However, there is no general preparative method of unsymmetrical 2(1H)-pyrimidinones. The author developed two new preparative methods of unsymmetrical 2(1H)-pyrimidinones.

(1) N-Phenylurea reacts with benzoylacetone derivatives to give mainly 1,4-diaryl-6-methyl-2(1H)-pyrimidinones, while N-phenylthiourea affords only 1,6-diaryl-4-methyl-2(1H)-pyrimidinethiones.

(2) The selective preparation of unsymmetrical 2(1H)-pyrimidinones is established by the reaction of β-aminoenones with aryl isocyanates.

Many papers have been reported on the optical resolution of rotational isomers caused by the restricted rotation around the carbon-carbon single bond since the optical resolution of 6,6'-dinitrophenoic acid was reported as the first example. In contrast few papers on the restricted rotation about the carbon-nitrogen single bond have been reported. Since 1-aryl-2(1H)-pyrimidinones are considered to be aza-analogues of biphenyl compounds, the author studied the structure and rotational isomerism around the carbon-nitrogen single bond.

(3) From PMR observation that C-6 methyl protons of 1-aryl-4,6-dimethyl-2(1H)-pyrimidinones resonates at higher field than those of 1,4,6-trimethyl-2(1H)-pyrimidinone due to the shielding effect of the aryl ring, the pyrimidine ring is found to be nearly perpendicular to the aryl ring in the most stable conformation. This fact is also supported by UV spectral evidence.

(4) The rotational barrier around the carbon-nitrogen single bond was calculated by means of Force-field method. The dihedral angle between the aryl and pyrimidine ring in the most stable conformation is 41°, and the rotational barrier is 39.5 kcal $mol^{-1}$ in the case of 4,6-dimethyl-1-(o-tolyl)-2(1H)-pyrimidinone (40).

(5) By recrystallization of the salts with D-camphor-10-sulfonic acid, the author succeeds in the optical resolution of two rotational isomers attributable to the restricted rotation around the carbon-nitrogen single bond in 1-(o-substituted)phenyl-4,6-dimethyl-2(1H)-pyrimidinones.

(6) Activation energy for racemization of optically active 2(1H)-pyrimidinones (40 and 42) is measured to be 31.8 and 34.0 kcal $mol^{-1}$, respectively and that of 2(1H)-pyrimidinethiones (48, 52, and 53) is 31.5, 30.1, and 31.1 kcal $mol^{-1}$, respectively.

(7) When the rotational barrier around the carbon-nitrogen single bond of 4,6-dimethyl-1-(o-tolyl)-2(1H)-pyrimidinone (40) is compared with that of the corresponding 2(1H)-pyrimidinethione (48), the rotational barrier of 40 is found to be nearly equal that of 48. This is caused by the contribution of the polarlized form as shown in Fig. 7.

1-Unsubstituted or 1-alkyl-2(1H)-pyrimidinones are known to exhibit various pharmaceutical activities such as tranquilizing or sedative activity. As an extensive study of 1-substituted 2(1H)-pyrimidinones, the antiinflammatory activity of 1-aryl-2(1H)-pyrimidinones and their D-camphor-10-sulfonates

was tested.

(8) Four kinds of 2(1H)-pyrimidinones (32, 40, 43, and 44) and two 2(1H)-pyrimidinethiones (48 and 49) exhibit potent antiinflammatory activity, but the safety area of these compounds is found to be narrow from the result of $LD_{50}$ value.

In Chapter III, the author investigates chemical reaction of 1-aryl-2(1H)-pyrimidinones. It is known that methyl protons are easily activated by the adjacent aromatic ring, especially nitrogen containing heteroaromatic ring. The deuterium exchange of methyl protons of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone (32) was carried out under basic conditions.

(9) C-6 Methyl protons are deutrated more easily than C-4 methyl protons in compound 32.

(10) Therefore, the regiospecific C-alkylation is tried. 4,6-Dimethyl-1-phenyl-2(1H)-pyrimidinone (32) was treated with alkyl halides in the presence of sodium hydride in DMF to afford the C-6 alkylated products, regiospecifically. However, the purification and reaction condition should be improved because of low yield.

(11) In the case of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinethione (36), the expected C-alkylation does not occur, but the corresponding 2(1H)-pyrimidinone (32) is obtained in 80% yield. Thus, it becomes possible to convert of thiocarbonyl into carbonyl group by the application of this reaction.

Although there have been many papers on electrophilic reaction, few papers concerning nucleophilic reaction of 2(1H)-pyrimidinones have been reported. Therefore, the author investigated the reaction of 1-aryl-2(1H)-pyrimidinones with various nucleophilic reagents.

(12) From the calculated atomic population by means of INDO method, it is expected that C-2, C-4, and C-6 carbon on the pyrimidine ring are easily attacked by nucleophiles.

(13) First, the reaction of 1-aryl-2(1H)-pyrimidinones with amines was attempted. 1,4,6-Trisubstituted 2(1H)-pyrimidinethiones undergo Dimroth type ring transformation with ammonia or primary alkyl amines in the presence of silver perchlorate to give 2-(N-substituted)aminopyrimidines or pyrimidinium perchlorates, respectively.

(14) In the case of hydroxylamine, 2(1H)-pyrimidinethiones also underdgo Dimroth type ring transformation to give a new type of 2-(N-substituted)aminopyrimidine 1-oxides. On the other hand, 2(1H)-pyrimidinones are transformed into 3,5-disubstituted isoxazoles in high yields.

(15) 4,6-Dimethyl-1-phenyl-2(1H)-pyrimidinone (32) reacts with methylmagnesium iodide to give 3,6-dihydro-4,6,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (137) selectively, while compound 32 reacts with methyl-lithium to yield mainly isomeric 3,4-dihydro-4,4,6-trimethyl-1-phenyl-2(1H)-pyrimidinone (138).

(16) It is ascertained that Grignard reagent attacks C-6 carbon more favorably than C-4 carbon, while organolithium reagent attacks predominantly C-4 carbon. Further, it is found that the bulkiness of the alkyl group of the Grignard reagents has a large influence on the ratio of the 3,4- and 3,6-dihydro-2(1H)-pyrimidinones.

(17) Finally, 1-aryl-2(1H)-pyrimidinones reacted eith metal hydride complexes. The regioselective preparation of 3,4- and 3,6-dihydro-, and tetrahydro-2(1H)-pyrimidinones is achieved by the controlled reduction

of the corresponding 2(1H)-pyrimidinones by using $NaBH_4$ or $LiAlH_4$ under various conditions. The ratio of the three products is found to be dramatically dependent on the reaction conditions and on the nature of C-4 and C-6 substituents in the pyrimidine ring.

Raney nickel has been widely applied for the desulfuration of heterocyclic thioamide and related compounds. Therefore, the author investigated the desulfuration of 2(1H)-pyrimidinethiones with Raney nickel.

(18) 1-Aryl-2(1H)-pyrimidinethiones are desulfurized with Raney nickel under hydrogen atmosphere to give 1,2-dihydropyrimidines.

Since little attention has been paid to the photochemical reaction of 2(1H)-pyrimidinones which are very similar to the pyrimidine bases, the photochemical reaction of 1,4,6-trisubstituted 2(1H)-pyrimidinones was studied.

(19) By irradiation of 1,4,6-trisubstituted 2(1H)-pyrimidinones in benzene with high-pressure mercury lamp, the photochemical electrocyclization products, 3,4,6-trisubstituted 2-oxo-1,3-diazabicyclo[2.2.0]hex-5-enes, are obtained. Although the bicyclo[2.2.0] system is generally unstable, these photo-products

are stable at room temperature.

As mentioned in (13)-(17), the regioselective preparation of three kinds of reduced 2(1H)-pyrimidinones is accomplished by the reaction of 2(1H)-pyrimidinones with organometallic reagents or metal hydride complexes. Since reduced 2(1H)-pyrimidinones have no longer six π-electrons in the ring, it is apparent that they have not the aromaticity of the pyrimidine ring. So reduced 2(1H)-pyrimidinones can be expected to exhibit the properties of enamines and cyclic ureas. Therefore, in Chapter IV, the author investigated the reaction and synthetic utility of reduced 2(1H)-pyrimidinones.

(20) 3,6-Dihydro-2(1H)-pyrimidinones easily undergo the ring opening reaction with hydroxylamine to afford the oximes in good yields. The isomeric 3,4-dihydro-2(1H)-pyrimidinones do not react under the same condition.

(21) 3,6-Dihydro-2(1H)-pyrimidinones are facilely oxidized with chloranil to afford the corresponding 2(1H)-pyrimidinones in high yields.

(22) Tetrahydro-2(1H)-pyrimidinones undergo the reductive ring opening reaction with $LiAlH_4$ under reflux in

benzene-THF to give N-aryl-2,4-diaminopentanes in good yields.

(23) Tetrahydro-2(1H)-pyrimidinones are treated with sodium nitrite to yield the corresponding 3-nitroso-2(1H)-pyrimidinones in good yields. By decomposition with potassium hydroxide in methanol, methyl N-substituted N-arylcarbamates and tetrahydro-3-aryl-1,3-oxazin-2-ones are obtained.

(24) 3,4- and 3,6-Dihydro-2(1H)-pyrimidinethiones are treated with methyl iodide in the presence of sodium hydride to give 2-methylthio-1,4- and 1,6-dihydropyrimidines, respectively, in high yields.

(25) 3,4- and 3,6-Dihydro-2(1H)-pyrimidinethiones are desulfurized with Raney nickel under reflux in methanol to give 1,4- and 1,6-dihydropyrimidines. From this result and (18), the selective synthesis of three types of dihydropyrimidine isomers is achieved by desulfuration with Raney nickel.

In conclusion, the research of 1-aryl-2(1H)-pyrimidinones provides the significant data for understanding the restricted rotation around the carbon-nitrogen single bond. This result is available for investigation of the restricted

rotation around the carbon-nitrogen single bond between pyrimidine bases and ribose moiety in nucleosides. Further, the author shows that 1-aryl-2(1H)-pyrimidinones are widely applicable for the transformation into many kinds of heterocyclic compounds and/or the preparation of chain compounds containing various functional groups.

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