The Nucleophilic Substitution of Methylthio Group on the 1,4-Dihydro-2-methylthiopyrimidine Rings

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N-Substituted 2-alkylthio-1,4-dihydro-4,4,6-trimethylpyrimidines easily reacted with methanol to give corresponding 2-methoxy-1,4-dihydropyrimidines, while the other nucleophiles did not react on the C-2 carbon of the pyrimidine rings. However, the substitution of alkylthio group easily proceeded intramolecularly even with weak nucleophilic groups, *e.g.*, phenolic oxygen, thiophenolic sulfur, and anilino nitrogen atom, to yield bi- or tricyclic pyrimidine derivatives.

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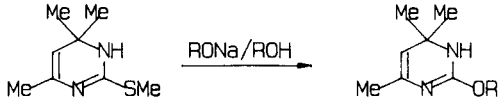
In previous papers, we discussed the reactivities and properties of various dihydropyrimidines. Dihydropyrimidine which has dimethylamino group in the C-2 position of the pyrimidine ring showed a unique characteristic. 1,6-Dihydro-4,6,6-trimethyl-2-dimethylaminopyrimidine caused [4 + 2] cycloaddition with acetylenic compound [1], and showed lower oxidation potential than the other 2-substituted dihydropyrimidines [2]. In order to prepare dihydropyrimidines having various substituents on the C-2 position of the pyrimidine ring, 2-methylthio substituted dihydropyrimidines were selected as starting materials because the alkylthio groups operate as good leaving groups. The reactivity of 2-alkylthio substituted dihydropyrimidines toward nucleophiles was only reported for primary ammonia [3] and amines [4] as nucleophiles. However, the products were sometimes the Dimroth-type ring transformed compounds [4], moreover the structures were not 2-aminodihydropyrimidines but pyrimidine-2(1*H*)-imines. Herein, we describe the nucleophilic reaction of 2-alkylthiodihydropyrimidines with various nucleophiles.

Results and Discussion.

When 1,4-dihydro-4,4,6-trimethyl-2-methylthio-1-phenylpyrimidine (**1**) was treated with sodium methoxide in methanol under reflux for 24 hours, methylthio group was easily substituted by methoxy group to yield 1,4-dihydro-2-methoxy-4,4,6-trimethyl-1-phenylpyrimidine (**7**), which was determined from spectral and microanalytical data. This substitution reaction proceeded even in the absence of a base. The same treatment of 2-alkylthio-1,4-dihydropyrimidines with methanol was carried out, and the results are summarized in Table 1. Among these results, 1,4-dihydro-4,4,6-trimethyl-1-(*p*-methylphenyl)-2-methylthiopyrimidine (**3**) reacted with sodium methoxide to give the corresponding 2-methoxy-1,4-dihydropyrimidine **8** in 76% yield, while 1,4-dihydro-4,4,6-trimethyl-1-(*o*-methylphenyl)-2-methylthiopyrimidine (**4**) yielded a product **9** in only 13% yield and 77% of the starting material was recovered though drastic reaction conditions were employed. When *p*-methylphenyl **3** and *o*-methylphenyl derivatives **4** were mixed and heated in methanol for 24 hours, a different reaction rate between the two compounds was observed. The ratio of the reaction rate was calculated from the yield to be $k_p/k_o = 4.2$ in this competitive reaction. Ethylthio group on 2-ethylthio-1,4-dihydropyrimidine **2** also retarded the substitution reaction by methanol comparing with methylthio group. These results demonstrated that steric hindrance existed around the C-2 carbon of the dihydropyrimidines and nucleophilic attack was prevented by the large substituent on the N-1 nitrogen.

N-Unsubstituted 1,6-dihydro-4,6,6-trimethyl-2-methylthiopyrimidine (**12**) also reacted with sodium methoxide and sodium ethoxide to afford 2-methoxy- **13** and 2-ethoxy-1,6-dihydropyrimidines **14** [2] in 50% yield, respectively (Scheme 1). However, *N*-substituted 1,4-dihydropyrimidine **1** did not react even with sodium ethoxide, and the starting material was recovered. Therefore, the difference in steric bulkiness between the methoxide and ethoxide anion affected the nucleophilic substitution of the *N*-substituted dihydropyrimidine **1**, and any other nucleophile also did not react on the C-2 carbon of the dihydropyrimidine ring.

Scheme 1



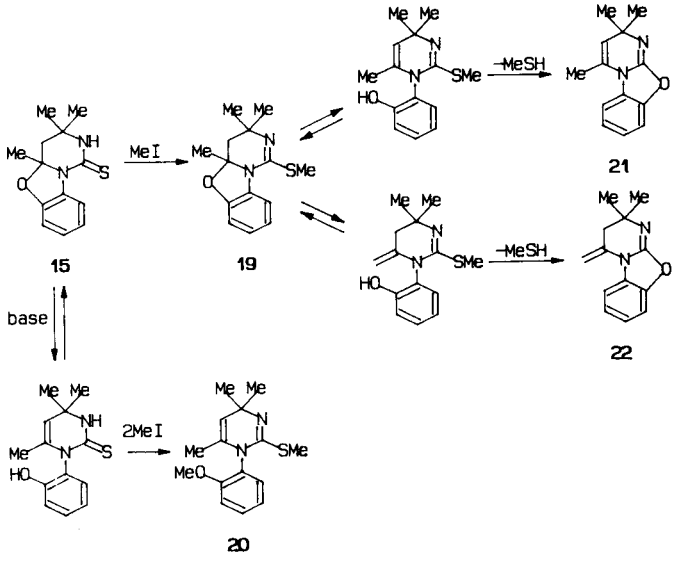
12 **13**: R=Me **14**: R=Et

In this way, nucleophilic substitution reaction of alkylthio group on the C-2 carbon of 2-alkylthio-1,4-dihydropyrimidines was retarded owing to the steric hindrance. Therefore, intramolecular substitution toward methylthio group was attempted.

3,4-Dihydropyrimidine-2(1*H*)-thiones which have nucleophilic substituent on the ortho position of the phenyl group on the N-1 nitrogen atom were prepared from the condensation of 4-isothiocyanato-4-methyl-2-pentanone and amines [5]. As reported in the literature [6-8], all these 3,4-dihydropyrimidine-2(1*H*)-thiones gave rise to intramolecular nucleophilic attack on the C-6 carbon of the pyrimidine ring to produce tricyclic heterocyclic systems. Pyrimidinethiones which have nucleophilic group on the β-position of the alkyl group on the N-1 nitrogen atom also gave bicyclic pyrimidinethiones [6a,7]. The methylation was attempted toward these pyrimidinethiones. Tetrahydrotrimethylthioxopyrimidobenzoxazole **15** was treated with sodium hydride in benzene at room temperature for 1 hour, and then methyl iodide was added under refluxing for 2 hours to give four products, the *S*-methylated compound **19** in 16% yield, 1,4-dihydro-1-(*o*-methoxyphenyl)-4,4,6-trimethyl-2-methylthiopyrimidine (**20**) [8] in 5% yield, and a 1:1 mixture of the tricyclic dihydropyrimidine **21** and its exo-methylene isomer **22** in 37% yield. The two isomers **21** and **22** could not be separated. When this methylation was carried out at room temperature, the yields of **19**, **20**, and the mixture of **21** and **22** were changed to 23%, 4%, and 1%, respectively. From this result, compound **19** was regarded to be the intermediate for **20**, **21**, and **22**. The structure of exo-methylene type compound **22** was elucidated from that of exo-methylene dihydropyrimidinethione isomer reported by Zigeuner *et al* [9].

The reaction mechanism was investigated by the ^{1}H-nmr spectral data. When tricyclic pyrimidinethione **15** was dissolved in methanol-d_4, no deuterium exchange was observed except the disappearance of the N-H peak. However, when compound **15** was dissolved in methanol-d_4 in the presence of sodium trideuteriomethoxide, the peak attributable to the olefinic proton appeared, the peak attributable to the methylene protons of **15** disappeared, and the absorption pattern of the aromatic protons changed. This observation suggested that the ring opening of the tricyclic pyrimidinethione by the cleavage between C-6 and O bond occurred in basic conditions to yield phenolic derivatives. This phenolic anion was methylated to yield 1,4-dihydro(*o*-methoxyphenyl)pyrimidine **20**. Furthermore, when the isolated *S*-methylated pyrimidine **19** was dissolved in deuteriochloroform, the compound **19** was changed to the mixture of pyrimidobenzoxazole derivatives **21** and **22**. The methylthio group on the dihydropyrimidine was able to be substituted with the phenolic oxygen atom even though the nucleophilicity was much weaker than the methoxide anion (Scheme 2).

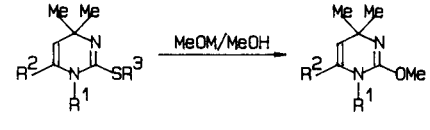
Scheme 2



Although thioxopyrimidobenzothiazole **16**, thioxopyrimidobenzimidazoline **17**, and thioxopyrimidoxazolidine **18** were methylated by methyl iodide under aprotic conditions in the presence of sodium hydride as described above, only *S*-methylated compounds **23**, **24**, and **25** were obtained in good yields, respectively. When the *S*-methylated compounds **23** and **24** were treated with potassium *t*-butoxide in *t*-butyl alcohol under reflux, a compound **26** which had an exo-methylene group and a compound **27**, whose structure was not determined whether dihydropyrimidine or pyrimidineimine, were obtained in 79% and 52% yield, respectively. It was shown that the methylthio group also substituted by weak nucleophiles, such as

Table 1

Reaction of 2-Alkylthio-1,4-dihydropyrimidines with Methanol

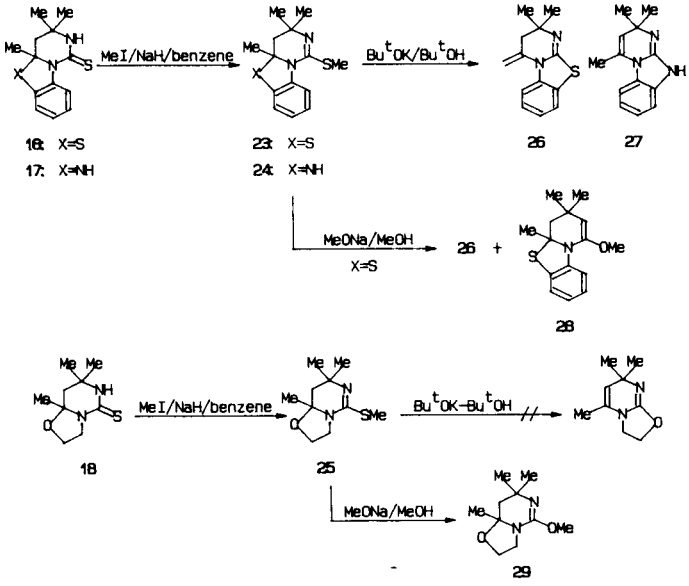


1: R^1=Ph, R^2=R^3=Me
2: R^1=Ph, R^2=Me, R^3=Et
3: R^1=*p*-MeC$_6$H$_4$, R^2=R^3=Me
4: R^1=*o*-MeC$_6$H$_4$, R^2=R^3=Me
5: R^1=*p*-MeOC$_6$H$_4$, R^2=R^3=Me
6: R^1=R^2=Ph, R^3=Me
7: R^1=Ph, R^2=Me
8: R^1=*p*-MeC$_6$H$_4$, R^2=Me
9: R^1=*o*-MeC$_6$H$_4$, R^2=Me
10: R^1=*p*-MeOC$_6$H$_4$, R^2=Me
11: R^1=R^2=Ph

Reactant	M	Time (day)	Product	Yield (%)	Recovery (%)
1	Na	1	**7**	76	5
1	H	1	**7**	64	20
2	Na	1	**7**	67	15
3	H	1	**8**	69	11
3	Na	2	**8**	76	tr
4	Na	3	**9**	13	77
5	H	1	**10**	80	5
5	Na	2	**10**	68	tr
6	Na	1	**11**	58	31

anilino nitrogen atom and thiophenolic sulfur atom. The formation of **26** and **27** can be explained by the ring-opening of the tricyclic compounds, followed by abstraction of the proton from the C-6 methyl group in the case of sulfur atom, while abstraction of the proton from the C-5 methylene group in the case of nitrogen atom. However, the substitution of methylthio group with an oxygen atom did not occur in the case of compound **25** (Scheme 3).

Scheme 3



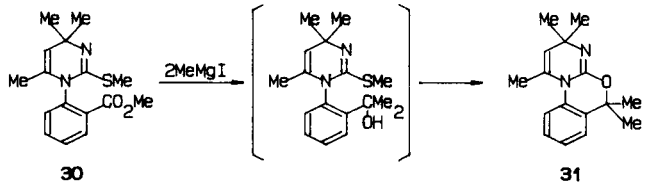
16: X=S
17: X=NH
23: X=S
24: X=NH
26
27
28
18
25
29

The intra- and intermolecular competitive reaction was attempted by the use of **23** with sodium methoxide in methanol. The compound **28** which was substituted methylthio group with methoxy group was obtained in 19% yield, while an intramolecularly cyclized product **26** was obtained in a yield of 36%. In this way, the intramolecular reaction proceeded faster than the intermolecular reaction. Compound **25**, which did not proceed through intramolecular substitution, reacted with sodium methoxide to yield intermolecularly substituted product **29** in 64% yield. It was shown that compound **25** had no equilibrium with ring opened form.

The Grignard reagents did not react with the *N*-aryl substituted dihydropyrimidines. However, 1,4-dihydro-1-(*o*-methoxycarbonylphenyl)-2-methylthiopyrimidine **30** reacted with methylmagnesium iodide to give tricyclic compound **31** (Scheme 4). This compound was formed by the reaction of methylmagnesium iodide on the methoxy carbonyl group to yield alcoholic intermediate, and further nucleophilic substitution of the hydroxyl group at C-2 position of the pyrimidine ring.

It was concluded that *N*-substituted 2-alkylthio-1,4-dihydropyrimidines did not react with nucleophiles other than methanol on the C-2 carbon owing to the steric hindrance around the electrophilic center of dihydropyrimidines. However, when nucleophilic substituents existed in the molecules, the substitution of the methylthio group easily occurred even with phenolic oxygen atoms, anilino nitrogen atoms, and thiophenolic sulfur atoms.

Scheme 4



30
31

EXPERIMENTAL

Melting points, determined on a Yanagimoto micro melting point apparatus, are uncorrected. The ir spectra were measured on a Jasco IRA-1 infrared spectrophotometer. The ^{1}H-nmr spectra were recorded on a Hitachi R-24 (60 MHz) and a JEOL-100 spectrometer (100 MHz) using tetramethylsilane as an internal standard. The ^{13}C-nmr spectra were obtained on a JEOL-100 spectrometer using tetramethylsilane as an internal standard.

Materials.

2-Alkylthiodihydropyrimidines were synthesized by alkylation of dihydropyrimidine-2(1*H*)-thiones [10]. Tricyclic and bicyclic dihydropyrimidine-2(1*H*)-thione derivatives were prepared by Mathes' method [7].

Thioxopyrimidobenzoxazole **15** [6a].

This compound had ir (potassium bromide): 3220, 1690 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 100 MHz, δ 1.43 (s, 3H), 1.46 (s, 3H), 1.64 (s, 3H), 2.33, 2.52 (ABq, 2H, J = 13.7 Hz), 6.7-7.2 (m, 3H), 7.3 (br s, 1H), 8.5-8.7 (m, 1H); ^{1}H-nmr tetradeuteriomethanol + sodium trideuteriomethoxide): 60 MHz, δ 1.36 (s, 6H), 1.62 (s, 3H), 4.75 (s, 1H), 6.2-7.7 (m, 4H); ^{13}C-nmr (deuteriochloroform): δ 24.1 (q), 29.8 (q), 32.9 (q), 45.4 (t), 51.7 (s), 97.5 (s), 109.3 (d), 117.5 (d), 121.1 (d), 124.9 (d), 130.0 (s), 149.5 (s), 173.0 (s).

Thioxopyrimidobenzothiazole **16** [5,6a].

This compound had ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.43 (s, 6H), 1.80 (s, 3H), 2.37, 2.74 (ABq, 2H, J = 13.2 Hz), 7.0-7.4 (m, 3H), 8.6-8.8 (m, 1H).

Thioxopyrimidobenzimidazole **17** [6a].

This compound had ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.37 (s, 6H), 1.50 (s, 3H), 2.16, 2.42 (ABq, 2H, J = 15.8 Hz), 5.4 (br s, 1H), 6.5-7.0 (m, 3H), 7.9 (br s, 1H), 8.6-8.8 (m, 1H).

Thioxopyrimidoxazoline **18** [6a,10].

This compound was recrystallized from ethanol, mp 187-188° (lit 180°); ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.37 (s, 6H), 1.49 (s, 3H), 1.88, 2.55 (ABq, 2H, J = 13.2 Hz), 3.6-4.7 (m, 2H), 7.5 (br s, 1H).

Reaction of 1,4-Dihydro-2-alkylthiopyrimidines with Methanol.

A solution of dihydropyrimidine (1 mmole) in the presence or absence of sodium methoxide (10 mmoles) in methanol (10 ml) was refluxed. The reaction mixture was diluted with water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was chromatographed on silica gel with hexane-acetone-diethylamine (75:5:1) mixture as eluent, then purified by the vacuum distillation or recrystallization.

1,4-Dihydro-2-methoxy-4,4,6-trimethyl-1-phenylpyrimidine (**7**).

This compound had ir (chloroform): 1690, 1630 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 100 MHz, δ 1.26 (s, 6H), 1.45 (d, 3H, J = 1.0 Hz), 3.58 (s, 3H), 4.53 (q, 1H, J = 1.0 Hz), 7.1-7.2 (m, 2H), 7.2-7.4 (m, 3H); ^{13}C-nmr (deuteriochloroform): δ 19.2 (q), 33.3 (q), 52.4 (s), 53.5 (q), 108.0 (d), 127.0 (d), 128.4 (d), 129.5 (d), 132.4 (s), 139.4 (s), 149.3 (s).

Picrate of **7**.

To a solution of **7** (2 mmoles) in ethanol (5 ml), the solution of picric acid (2 mmoles) in ethanol (5 ml) was added. After standing for 15 hours, the resulting crystal was collected and recrystallized from ethanol, mp 157-159°.

Anal. Calcd. for $C_{20}H_{21}N_5O_8$: C, 52.28; H, 4.60; N, 15.24. Found: C, 52.27; H, 4.62; N, 15.18.

1,4-Dihydro-2-methoxy-4,4,6-trimethyl-1-(*p*-methylphenyl)pyrimidine (**8**).

This compound was recrystallized from hexane, mp 45-46°; bp 37°/10^{-4} mm Hg; ir (chloroform): 1680, 1630 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.23 (s, 6H), 1.43 (d, 3H, J = 1.0 Hz), 2.32 (s, 3H), 3.55 (s, 3H), 4.50 (q, 1H, J = 1.0 Hz), 6.9-7.2 (m, 4H).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.46. Found: C, 73.75; H, 8.39; N, 11.44.

1,4-Dihydro-2-methoxy-4,4,6-trimethyl-1-(*o*-methylphenyl)pyrimidine (**9**).

This compound had bp 121°/5 mm Hg, ir (chloroform): 1690, 1680 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.27 (s, 6H), 1.37 (d, 3H, J = 7.0 Hz), 2.20 (s, 3H), 3.60 (s, 3H), 4.53 (q, 1H, J = 7.0 Hz), 7.1-7.4 (m, 4H).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.68; H, 8.29; N, 11.48.

1,4-Dihydro-2-methoxy-1-(*p*-methoxyphenyl)-4,4,6-trimethylpyrimidine (**10**).

This compound had bp 43°/10^{-2} mm Hg, ir (chloroform): 1680, 1630 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.23 (s, 6H), 1.43 (d, 3H, J = 1.0 Hz), 3.58 (s, 3H), 3.79 (s, 3H), 4.52 (q, 1H, J = 1.0 Hz), 6.9-7.3 (m, 4H).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.96; H, 7.78; N, 10.70.

1,4-Dihydro-2-methoxy-4,4-dimethyl-1,6-diphenylpyrimidine (**11**).

This compound was recrystallized from hexane, mp 100-101°; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.53 (s, 6H), 3.68 (s, 3H), 5.13 (s, 1H), 7.10 (s, 10H).

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.66; H, 6.86; N, 9.52.

1,6-Dihydro-2-methoxy-4,6,6-trimethylpyrimidine (**13**).

This compound was recrystallized from hexane, mp 93-94°; bp 108°/20 mm Hg; ir (chloroform): 3400, 1700, 1650 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.20 (s, 6H), 1.78 (d, 3H, J = 1.0 Hz), 3.73 (s, 3H), 4.46 (q, 1H, J = 1.0 Hz), 4.7 (br s, 1H).

Anal. Calcd. for $C_9H_{14}N_2O$: C, 62.30; H, 9.15; N, 18.16. Found: C, 62.16; H, 9.22; N, 18.09.

Competition Reaction of **3** and **4**.

Compounds **3** (1 mmole) and **4** (1 mmole) were mixed in a methanol solution, and refluxed for 24 hours. The crude product was treated according to the same manner described above. The products **8** and **9** could not be separated. Therefore, the crude product was purified by column chromatography on silica gel with hexane-acetone-diethylamine (75:5:1) mixture as eluent. The ratio of yield was determined from the ^{1}H-nmr spectrum.

Methylation of Tricyclic or Bicyclic Dihydropyrimidine-2(1*H*)-thione Derivatives.

Pyrimidinethione (3 mmoles) was stirred for 1 hour in benzene (20 ml) in the presence of sodium hydride (15 mmoles), and then methyl iodide (10 mmoles) in benzene (10 ml) was added dropwise to the mixture. After refluxing for 2 hours, the reaction mixture was washed with water, then the organic layer was dried over magnesium sulfate. After the solvent was evaporated, the crude product was chromatographed on silica gel with hexane-acetone-diethylamine (50:5:1) mixture as eluent.

Methylthiopyrimidobenzoxazole (**19**).

This compound had ir (chloroform): 1700, 1590 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 100 MHz, δ 1.20 (s, 3H), 1.30 (s, 3H), 1.50 (s, 3H), 2.19 (s, 2H), 2.36 (s, 3H), 6.7-7.0 (m, 3H), 7.4-7.6 (m, 1H); ^{13}C-nmr (deuteriochloroform): δ 26.4 (q), 29.9 (q), 31.9 (q), 44.6 (q), 53.3 (t), 98.3 (s), 109.5 (d), 116.4 (d), 120.5 (d), 123.8 (s), 131.5 (s), 149.5 (s), 151.1 ppm (s).

Pyrimidobenzoxazole (Mixture of **21** and **22**).

These compounds had ir (chloroform): 1690 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 100 MHz, δ 1.26 (s, 6H), 1.31 (s, 6H), 2.25 (d, 3H, J = 1.5 Hz), 2.32 (s, 2H), 4.58 (d, 1H, J = 1.5 Hz), 4.66 (d, 1H, J = 1.0 Hz), 5.04 (br s, 1H), 6.8-7.3 (m, 8H); ^{13}C-nmr (deuteriochloroform): δ 18.5 (q), 29.2 (q), 33.1 (q), 40.8 (t), 52.3 (s), 55.4 (s), 95.6 (t), 109.4 (d), 110.5 (d), 121.6 (d), 122.4 (d), 123.1 (d), 128.6 (s), 130.0 (s), 137.4 (s), 144.5 (s), 144.9 (s), 150.3 (s), 151.1 ppm (s).

Picrate of Mixture of **21** and **22**.

To a solution of the mixture of **21** and **22** (2 mmoles) in ethanol (5 ml), the solution of picric acid (2 mmoles) in ethanol (5 ml) was added. After standing for 15 hours, the resulting crystals were collected and recrystallized from water-ethanol, mp 139° dec.

Anal. Calcd. for $C_{19}H_{17}N_5O_8$: C, 51.47; H, 3.86; N, 15.79. Found: C, 51.42; H, 3.85; N, 15.74.

Methylthiopyrimidobenzothiazole **23**.

This compound was obtained in 75% yield and recrystallized from hexane, mp 114-115°; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.26 (s, 3H), 1.33 (s, 3H), 1.67 (s, 3H), 2.22 (s, 2H), 2.26 (s, 3H), 6.8-7.3 (m, 3H), 7.3-7.6 (m, 1H).

Anal. Calcd. for $C_{14}H_{18}N_2S_2$: C, 60.39; H, 6.51; N, 10.06. Found: C, 60.61; H, 6.64; N, 10.02.

Methylthiopyrimidobenzimidazole **24**.

This compound was obtained in 87% yield and recrystallized from hexane, mp 78-79°; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.20 (s, 3H), 1.32 (s, 3H), 1.45 (s, 3H), 2.08 (br s, 2H), 2.40 (s, 3H), 3.9 (br s, 1H), 6.5-6.9 (m, 3H), 7.4-7.6 (m, 1H).

Anal. Calcd. for $C_{14}H_{19}N_3S$: C, 64.33; H, 7.32; N, 16.07. Found: C, 64.31; H, 7.33; N, 16.11.

Methylthiopyrimidoxazoline **25**.

This compound was obtained in 90% yield, ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.20 (s, 6H), 1.34 (s, 3H), 1.63, 2.06 (ABq, 2H, J = 12.8 Hz), 2.30 (s, 3H), 3.3-4.0 (m, 4H).

Reaction of Methylthiopyrimidine Derivatives with *t*-Butyl Alcohol.

A solution of dihydropyrimidine (1 mmole) in the presence of potassium *t*-butoxide (2 mmoles) in *t*-butyl alcohol (10 ml) was refluxed. The reaction mixture was diluted with water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was chromatographed on silica gel with hexane-acetone-diethylamine (50:5:1) mixture as eluent.

Pyrimidobenzothiazole **26**.

This compound was recrystallized from hexane, mp 70-71°; ir (chloroform): 1600 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.22 (s, 6H), 2.24 (s, 2H), 4.80 (s, 1H), 5.12 (s, 1H), 6.8-7.5 (m, 4H).

Anal. Calcd. for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.12; N, 12.16. Found: C, 67.83; H, 6.18; N, 12.12.

Pyrimidobenzimidazole **27**.

This compound was recrystallized from 2-propanol, mp 211-212°;

^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.43 (s, 6H), 2.42 (s, 3H), 4.78 (s, 1H), 6.9-7.6 (m, 4H).

Anal. Calcd. for $C_{13}H_{15}N_3 \cdot 0.2H_2O$: C, 72.07; H, 7.21; N, 19.01. Found: C, 71.98; H, 7.00; N, 19.38.

Reaction of Methylthiopyrimidine Derivatives with Methanol.

A solution of dihydropyrimidine (1 mmole) in the presence of sodium methoxide (10 mmoles) in methanol (20 ml) was refluxed. The reaction mixture was diluted with water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was chromatographed on silica gel with hexane-acetone-diethylamine (50:5:1) mixture as eluent.

Methoxypyrimidobenzothiazole **28**.

This compound was recrystallized from hexane, mp 103-104°; ir (chloroform): 1620 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 100 MHz, δ 1.31 (s, 3H), 1.35 (s, 3H), 1.83 (s, 3H), 1.7-2.5 (m, 2H), 3.07 (s, 3H), 6.8-7.7 (m, 4H); ^{13}C-nmr (deuteriochloroform): δ 25.9 (q), 29.8 (q), 32.7 (q), 40.9 (t), 49.1 (q), 53.7 (s), 87.7 (s), 113.1 (d), 121.5 (d), 122.5 (s), 125.6 (s), 125.6 (d), 138.6 (s), 155.5 (s).

Anal. Calcd. for $C_{18}H_{18}N_2OS$: C, 64.09; H, 6.94; N, 10.67. Found: C, 63.89; H, 6.96; N, 10.60.

Methoxypyrimidoxazoline **29**.

This compound was obtained in 64% yield, bp 123°/20 mm Hg; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.16 (s, 3H), 1.20 (s, 3H), 1.36 (s, 3H), 1.55, 2.02 (ABq, 2H, J = 13.6 Hz), 3.3-4.1 (m, 4H).

Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.12. Found: C, 60.26; H, 9.18; N, 14.05.

Reaction of **30** with Methylmagnesium Iodide.

To a solution of methylmagnesium iodide (10 mmoles) in ether (20 ml), a solution of dihydropyrimidine (1 mmole) in ether (10 ml) was added under nitrogen atmosphere. The solution was stirred for 3 hours at room temperature. The reaction mixture was diluted with water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was chromatographed on silica gel with hexane-acetone-diethylamine (16:6:1) mixture as eluent, then purified by vacuum distillation and recrystallization from hexane. Compound **31** was obtained in 44% yield, bp 155°/5 mm Hg; mp 167-168°; ir (potassium bromide): 1670, 1700 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 1.26 (s, 6H), 1.66 (s, 6H), 1.96 (s, 3H), 5.04 (s, 1H), 6.7-7.6 (m, 4H).

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.92. Found: C, 74.85; H, 7.89; N, 10.88.

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