PhS$^+$, 92 (20), 91 (100). **9**: n^{18}_D 1.6390; ^{1}H NMR ($CDCl_3$, 0.1 M, 250 MHz) 1.41 (d, J = 11 Hz, 1 H, H-7a), 1.47 (m, 3 H, H-1, H-2, H-6), 2.07 (d, J = 11 Hz, 1 H, H-7b), 2.09 (s, 1 H, H-4), 3.37 (s, 1 H, H-5), 4.00 (s, 1 H, H-3), 7.09–7.47 (aromatic protons); ^{13}C NMR ($CDCl_3$, 0.14 M, 62.89 MHz) 13.44, 16.17, 17.85 (C-1, C-2, C-6), 30.64 (C-7), 39.68 (C-4), 50.19 (C-3), 53.98 (C-5), 125.89, 126.64, 128.85, 128.93, 129.60, 131.02, 136.78; MS EI, m/z (relative intensity) 312 (3), 311 (7), 310 (28) M$^+$, 244 (7.5), 202 (8), 201 (47) M$^+$ – PhS, 200 (9) M$^+$ – PhSH$^+$, 168 (6), 167 (4), 147 (5), 135 (12.5), 134 (9), 123 (22), $C_7H_7S^+$, 109 (10) PhS$^+$, 92 (17), 91 (100).

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Structures of Pyrimidine Derivatives Produced by Condensation of Ethyl Cyanoacetate with Methylguanidine. Evidence for the Presence of an Imino Tautomer

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The reaction of ethyl cyanoacetate with methylguanidine produced two unexpected side products, in addition to previously described products, 2,6-diamino-1-methyl-4(1*H*)-pyrimidinone and 6-amino-2-(methylamino)-4-(3*H*)-pyrimidinone. The presence of an isomer of the 1-methylpyrimidine derivative was presumed on the basis of the appearance of the NMR spectra differing from that of the 1-methylpyrimidine derivative in an aprotic neutral solvent. The unexpected major product was identified as 2,6-diamino-4(3*H*)-pyrimidinone, while the minor one was in two tautomeric forms, 6-amino-1-methyl-2-(methylamino)-4(1*H*)-pyrimidinone and 6-amino-1-methyl-2-(methylimino)-1,2-dihydro-4(3*H*)-pyrimidinone. Such amino–imino tautomerization depended on a polarity of solvent and its temperature. The formation of the above two unexpected products was most probably due to the reaction of ethyl cyanoacetate with guanidine and dimethylguanidine that were formed as side products in the preparation of methylguanidine. However, a Watanabe-type N_1–C_2–N_3 replacement on the 1-methylpyrimidine derivative could not be neglected as an alternative mechanism for the formation of the diaminopyrimidine derivative. The Dimroth-type rearrangement of the 1-methylpyrimidine derivative to its 2-(methylamino) isomer occurred by catalytic action of either methylamine or guanidine under similar conditions.

In connection with the structural determination of pigments isolated from the skin of *Rhacophorus arboreus*,[1] we needed to prepare pyrimidine derivatives by condensation of ethyl cyanoacetate with methylguanidine. This condensation has been described to produce two monomethylpyrimidine derivatives, **1** and **3**.[2,3] Structure **2a** was assigned to the same product (**1**) in another reference.[4] The present paper is concerned with a reinvestigation of a literature method for the synthesis of methylguanidine and its subsequent condensation with ethyl cyanoacetate. We have now established the following four points: (i) The structures of the products reported in the literature[2-4] were structure **2a** and structure **3**, respectively. In addition, on the basis of appearance of the NMR spectra differing from that of **2a** in an aprotic solvent, the presence of an isomer (**2b**) of **2a** was presumed. (ii) The structure of the unexpected major product was structure **4** and the minor one was in two tautomeric forms **5a** and **5b**. Structure **5b** is a normally disfavored imino tautomeric form. (iii) The tautomerization of the five pyrimidine derivatives in solution depended on solvent polarity and temperature. In addition, a methyl substituent on nitrogen atoms in the pyrimidine nuclei was an important factor for stabilization of an imino tautomeric structure. (iv) The formation of the two unexpected products (**4** and **5**) was most probably caused by reaction of ethyl cyanoacetate with guanidine and dimethylguanidine, respectively, which were concomitantly formed in the preparation of methylguanidine. However, a Watanabe-type N_1–C_2–N_3 replacement[5] on **2a** with guanidine could not be neglected as an alternative mechanism for the formation of **4**. In addition, the formation of the expected product (**3**) was caused by a Dimroth-type rearrangement[6,7] on **2a** with both methylamine and guanidine.

Results and Discussion

Structures of Pyrimidines. Following the method reported for the preparation of monomethylpyrimidines,[2] ethyl cyanoacetate was condensed with methylguanidine obtained by fusion of dicyanodiamide with a large excess of methylamine. An expected major product (**2a**) (33% yield) was obtained as a precipitate and easily separated from the other products by filtration. Silica gel column chromatography of the filtrate afforded another expected product (**3**). However, its yield was very low (4%) in

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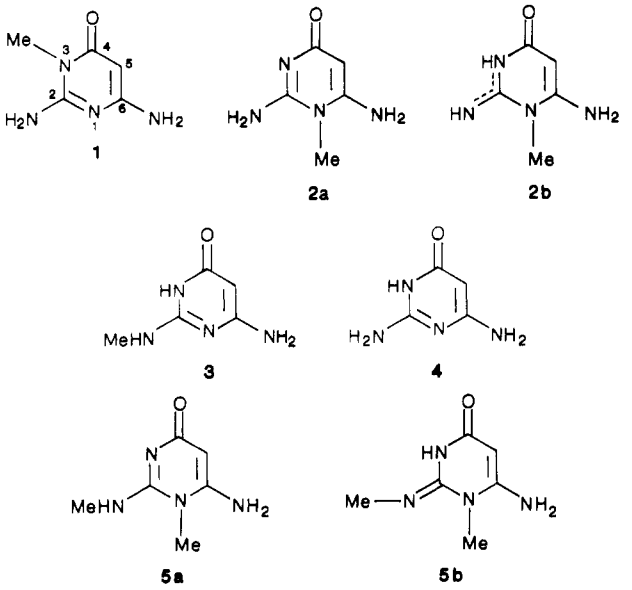

contrast to the yield (40%) described in the literature.[2-4] We therefore searched for the presence of the other products and found the two unexpected products (4 and 5) as well as an isomer (**2b**) of **2a**.

Product 2a. The physical data of the expected major product was completely identical with those reported in the literature.[2-4] The ^1H NMR chemical shifts of this product were not identical with the data[8] reported for the 3-methylpyrimidine derivative (1) that had been prepared from 2,6-diamino-5-iodo-3-methyl-4(3*H*)-pyrimidinone, suggesting the location of its methyl substituent on N-1 rather than N-3. The structure of the product was finally established by X-ray crystallography of its hemisulfate as shown in the ORTEP drawing in Figure 1. Thus, the major expected product was unambiguously assigned to 2,6-diamino-1-methyl-4(1*H*)-pyrimidinone (**2a**). Its ^1H and ^{13}C NMR spectra in several solvents were also best fitted to this structure, as described below.

Product 3. The identity of the expected minor product (3.9%) with 6-amino-2-(methylamino)-4(3*H*)-pyrimidinone (**3**) was indicated by coincidence of the melting point with the reported one[2,3] and then confirmed by complete interpretation of its NMR and MS spectra.

Product 4. An unexpected major product (35.4%) was identified with 2,6-diamino-4(3*H*)-pyrimidinone (**4**) by comparison and interpretation of its NMR and MS spectra.

An Isomer (2b) of 2a. The hemisulfate of an unexpected minor product (1.9%) showed the same ORTEP drawing as that of the hemisulfate of the expected major product (**2a**) on X-ray analysis. However, the ^1H and ^{13}C NMR spectra of this minor product in an aprotic solvent and its physical data clearly differed from those of the product (**2a**), suggesting the minor product to be an isomer (**2b**) of (**2a**). Table I shows the assignments for the ^{13}C NMR spectra of the above five products **2a**, **2b**, **3**, **4**, and **5** in an aprotic solvent (DMSO-d_6). The chemical shifts of C-2, C-4, C-5, and C-6 in the product **4** coincided with those of the corresponding carbons of the product **3**. Since a lactam form (4(3*H*)-one form)[9] had been assigned to the product **4** as a most stable tautomeric form, a similar lactam form should be assigned to the product **3** in this solvent. The ^{13}C NMR spectrum of the product **2a** is

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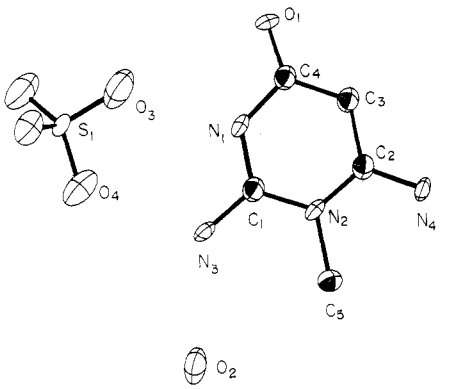

Figure 1. ORTEP drawing of the hemisulfate of the product **2a**.

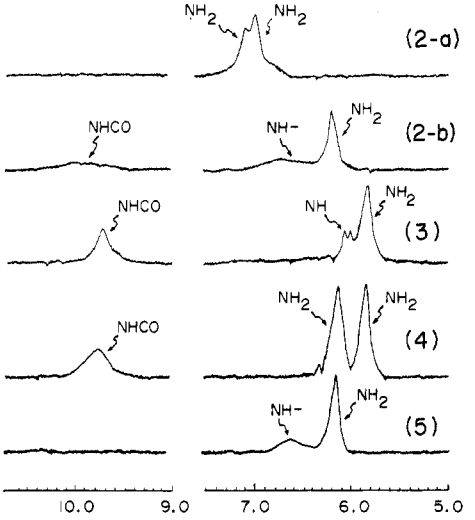

Figure 2. Amino and amido proton signals in the ^1H NMR spectra of the products **2a**, **2b**, **3**, **4**, and **5**.

Table I. ^{13}C NMR (DMSO-d_6) Spectral Assignments for the Products 2a, 2b, 3, 4, and 5

products	C-2	C-4	C-5	C-6	Me
2a	156.2	167.0	78.5	154.4	31.6
2b	154.8[a]	169.4	80.4	154.1[a]	30.9
3	163.4	165.1	76.4	154.9	27.1
4	163.2	165.3	76.4	155.3	
5	154.4[a]	170.4	79.1	153.3[a]	28.6, 30.4

[a] These assignments are interchangeable.

Table II. ^{13}C NMR (DMSO-d_6-D_2O = 2:1) Spectral Assignments for the Products 2a, 2b, 3, 4, and 5

products	C-2	C-4	C-5	C-6	Me
2a	156.9[b]			156.9[b]	32.7[b]
2b	156.2	173.4	82.2	156.2	32.3
3	165.6	166.3	77.5	155.6	28.0
4	165.3	166.3	77.8	156.0	
5	156.4[a]	173.7	80.8	155.1[a]	29.4, 31.7

[a] These assignments are interchangeable. [b] Definite data were not obtained for lack of solubility in this solvent.

Table III. ^{13}C NMR (2.8% NH_4OH in D_2O) Spectral Assignments for the Products 2a, 2b, 3, 4, and 5

products	C-2	C-4	C-5	C-6	Me
2a	157.8[a]	175.4	83.0	157.3[a]	32.9
2b	157.9[a]	175.4	82.8	157.4[a]	32.8
3	167.4	173.2	80.0	161.4	29.1
4	167.3	173.1	80.5	162.0	
5			82.1[b]		32.4[b], 30.0[b]

[a] These assignments are interchangeable. [b] Definite data were not obtained for lack of solubility in this solvent.

distinguished from those of the other four products. Table II shows the assignments for the ^{13}C NMR spectra of these five products in a protic neutral solvent (DMSO-d_6–D_2O = 2:1). On the basis of the chemical shifts of C-2, C-4, C-5, and C-6 on the pyrimidine nuclei, these products could be differentiated into the following two types: (a) the products **2a**, **2b**, and **5**; (b) the products **3** and **4**. A similar result was also observed for the ^{13}C NMR assignments of these products in a basic solvent (2.8% NH_4OH in D_2O), as shown in Table III. The physical and spectral data of the material recovered from the basic solution of the product **2b** by lyophilization completely coincided with those for the product **2a**, suggesting that the product **2a** is in a more stable tautomeric form than that of its isomer **2b**. These findings indicate that the structure of the product **2b** is in conformity with that of the product **2a** in both the protic neutral and the basic solvents. Accordingly, the product **2b** is likely to be in the form of an isomer of **2a**.

The isomeric structure of **2b** in solution was further elucidated by NMR study of amino and amido protons as follows. Since the C-4 ^{13}C signals of all the products appeared in an area similar to those of the carbonyl carbon signals of acylguanidines,[10] which correspond to a N_1–C_2–N_3–C_4 moiety of pyrimidine nuclei, the carbons at the 4-position on the pyrimidine nuclei of all the products were assigned to a carbonyl carbon. Accordingly, the structures of the product **2a** and its isomer **2b** were determined to be in a keto form. Figure 2 shows amino and amido proton signals in the ^1H NMR spectra of the products **2a**, **2b**, **3**, **4**, and **5** in an aprotic solvent (DMSO-d_6). Two amino proton signals of the product **2a** appeared at δ 6.98 and 7.09 as a broad singlet (4 H). Thus, such a 4(1*H*)-one form as structure **2a** was indicated for this product as a most stable tautomeric form. However, an amino proton signal corresponding to the amino proton at δ 6.98 of the product **2a** appeared at δ 6.18 as a broad singlet in the ^1H NMR spectrum of its isomer **2b**. In place of another amino proton signal of the product **2a** at δ 7.09, a very broad signal appeared at δ 6.67 for the isomer **2b**. Its integral ratio to the amino proton signal at δ 6.18 was 1:2. The amido (N-3) proton on the pyrimidine nuclei of the isomer **2b** exhibited a very broad signal near δ 10.0, in contrast to a broad singlet signal of the corresponding proton of the products **3** and **4** near δ 9.8. These findings suggest that a hydrogen atom in the pyrimidine nuclei of the isomer **2b** probably migrates between two nitrogen atoms, 2-NH and N(3). The ^1H NMR spectrum of the isomer **2b** in DMSO-d_6 did not change at 35 °C after 24 h. However, this spectrum clearly changed by addition of D_2O (or H_2O) to DMSO-d_6.

Figure 3 shows the solvent-dependent ^1H NMR spectra of the isomer **2b**. The aromatic (C-5) proton signal of the isomer **2b** in DMSO-d_6 appeared at δ 4.60 as a singlet, while that of the product **2a** appeared at δ 4.90 as a singlet. The former signal was shifted to a lower field with the addition of D_2O (or H_2O) to DMSO-d_6. Its chemical shift finally coincided with that of the corresponding proton of the product **2a**. These findings suggests that the isomer **2b** is probably in an equilibrium state between an amino tautomeric form **2a** and another tautomeric form in DMSO-d_6 solution, and this equilibrium lies to the amino form side with an increase in the ratio of D_2O (or H_2O) to DMSO-d_6. Accordingly, the structure of the isomer **2b** in an aprotic solvent was presumed to be a tautomeric structure as shown in structure **2b**, which resulted from migration of a hydrogen atom between the two nitrogen atoms at 2- and 3-positions.

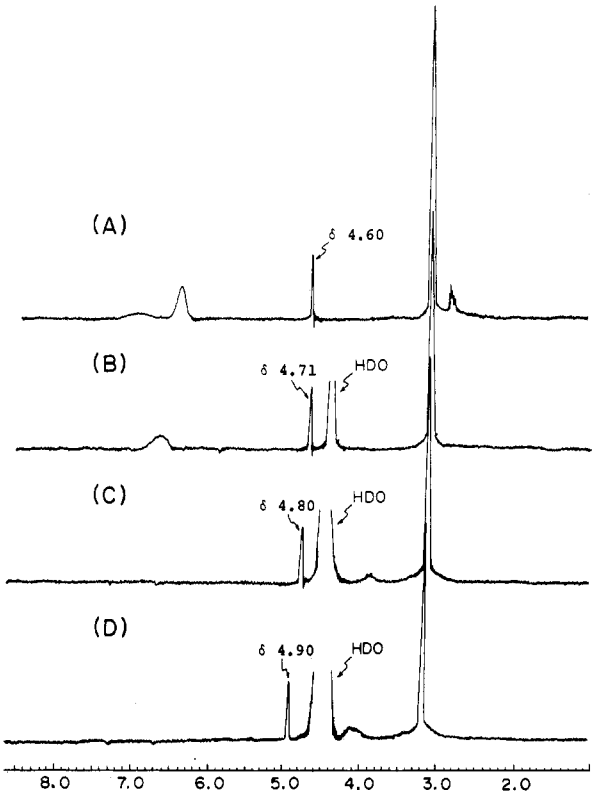

Figure 3. Solvent-dependent ^1H NMR spectra of the product **2b**: (A) DMSO-d_6; (B) DMSO-d_6–D_2O (300:1 v/v); (C) DMSO-d_6–D_2O (5:1 v/v); (D) D_2O.

Product 5. The unexpected minor product **5** (3.5%) exhibited UV and IR spectra characteristic of methylpyrimidines and the mass spectral fragmentation pattern suggestive of a dimethylpyrimidine derivative. Its ^1H NMR spectrum in DMSO-d_6 showed two methyl proton signals at δ 3.17 (3 H, s) and 2.70 (3 H, br d, J = 2 Hz) and two amino proton signals at δ 6.03 (2 H, br s) and 6.66 (1 H, br d). Irradiation of the amino proton signal at δ 6.66 caused the broad doublet at δ 2.70 to change to a singlet. Accordingly, these signals were assigned to a methylamino proton. The feature of the methylamino proton signals of the product **5**, however, clearly differed from those of the corresponding proton signals of the product **3**, suggesting that the product **5** is likely to be in an equilibrium state between two tautomeric forms. The tautomerization of the product **5** in solution was elucidated by NMR studies as follows.

Solvent-Dependent Tautomerization. Figure 4 shows the solvent-dependent ^1H NMR spectra of the product **5**. A feature of the methylamino proton signals of the product **5** clearly changed with a change in the ratio of $CDCl_3$ to DMSO-d_6. The broad doublet of the methyl proton signal changed to a singlet via a broad singlet with an increase in the ratio of $CDCl_3$ to DMSO-d_6. On the other hand, a broad signal of the amino proton at δ 6.09 changed to a very broad one in DMSO-d_6–$CDCl_3$ (5:1) and finally disappeared in DMSO-d_6–$CDCl_3$ (3:1). An amido (N-3) proton signal of the pyrimidine nuclei appeared at δ 10.17 as a very broad one in DMSO-d_6–$CDCl_3$. These findings can be explained by a change in the ratio of the tautomers between the —NHMe and =NMe groups of the product **5**. A methylamino form should be predominate in

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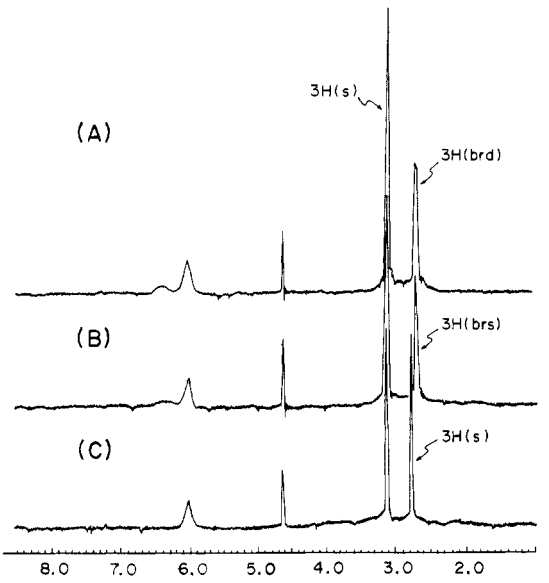


Figure 4. Solvent-dependent ^1H NMR spectra of the product **5**: (A) DMSO-d_6; (B) DMSO-d_6–$CDCl_3$ (5:1 v/v); (C) DMSO-d_6–$CDCl_3$ (3:1 v/v).

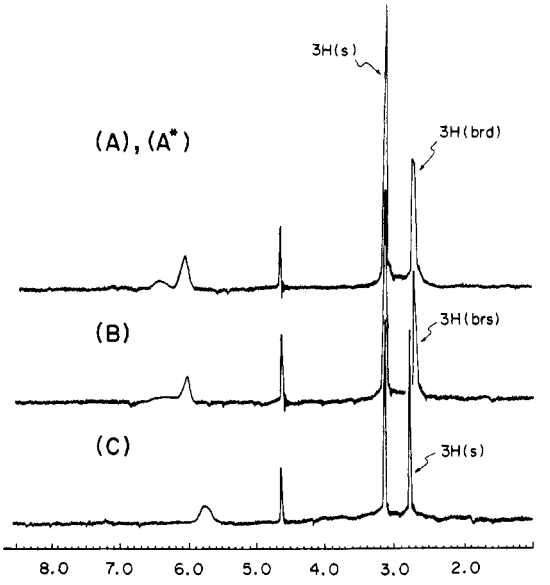
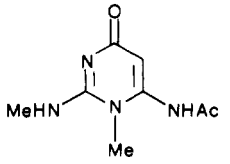


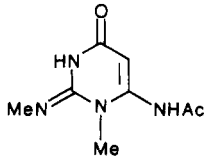
Figure 5. Temperature-dependent ^1H NMR spectra of the product **5**: (A) 35 °C; (A*) regenerated spectrum by cooling; (B) 60 °C, (C) 100 °C.

DMSO-d_6, and a methylimino form in DMSO-d_6–$CDCl_3$. Moreover, a methylamino form was probably predominant in protic neutral and basic solvents, since ^{13}C chemical shifts of the C-2, C-4, C-5, and C-6 of the product **5** coincided with those of the corresponding carbons of the product **2a** (Tables II and III). These findings indicate that the product **5** is in two tautomeric forms, **5a** and **5b**, in solution. This similar amino–imino tautomerization was also observed in the monoacetate **6** of the product **5**. A feature of the methylamino proton signal of the monoacetate **6** clearly changed on addition of $CDCl_3$ to DMSO-d_6. The doublet of the methyl proton signal changed to a singlet via a broad singlet with an increase in the ratio of $CDCl_3$ to DMSO-d_6. On the other hand, a broad doublet of the amino proton at δ 7.00 changed to a broad singlet in DMSO-d_6–$CDCl_3$ (2:1) and finally disappeared in DMSO-d_6–$CDCl_3$ (1:1). These findings indicate that the monoacetate **6** is in two tautomeric forms, **6a** and **6b**, in solution, which supports product **5** being in two tautomeric forms, **5a** and **5b**, in solution.

Consequently, the bis(methylamino)pyrimidine derivatives **5** and **6** are in an equilibrium state between the amino tautomeric form and the imino tautomeric form in solution. This equilibrium probably lies to the imino form side with a decrease in the polarity of solvent. On the other hand, no amino–imino tautomerization similar to these of the compounds **5** and **6** at room temperature was observed with the other pyrimidine derivatives **2a**, **2b**, **3**, and **4** under similar conditions. However, an amino–imino tautomerization took place on the product **3** as well as the product **5** on heating as follows.



6a



6b

Thermal Tautomerization. Figure 5 shows the temperature-dependent ^1H NMR spectra of the product **5** in DMSO-d_6. A feature of the methylamino proton signal of the product **5** clearly changed with a rise in temperature. The broad doublet of the methyl proton signal changed to a singlet with a rise in temperature. On the other hand, the broad signal of the amino proton changed to a very broad one at 60 °C and finally disappeared at 100 °C. The ^1H NMR spectrum of **5** at 60 °C was seemingly coincident with that of the same product in DMSO-d_6–$CDCl_3$ (5:1) (Figure 4). A feature of the other amino (6-NH_2) proton signal was not changed in the range of 35 to 60 °C though it was changed to a more broad one, suggesting that this amino proton tends to migrate at 100 °C. Since the chemical shift of the C-4 ^{13}C signal changed very little in the range of 35 to 60 °C (Tables I and IV), the carbon at the 4-position on the pyrimidine nuclei of **5** was assigned to a carbonyl carbon. Accordingly, these findings can be explained by a change in the ratio of the tautomers between the methylamino form (**5a**) and the methylimino form (**5b**). The equilibrium between the amino and imino tautomers lies to the imino tautomer side with a rise in temperature.

Table IV. ^{13}C NMR (DMSO-d_6, 60 °C) Spectral Assignments for the Products 2a, 2b, 3, 4, and 5

products	C-2	C-4	C-5	C-6	Me
2a	156.5	168.0	80.2	154.1	31.0
2b	154.9	168.3	80.1	153.7	30.4
3	166.1	166.1	77.3	155.9	27.3
4	164.0	166.1	77.0	156.3	
5	155.3	170.0	81.0	155.3	29.0, 30.5

Tautomerization similar to this was also observed with the 2-(methylamino)pyrimidine derivative **3** under similar conditions. Figure 6 shows the temperature-dependent ^1H NMR spectra of the product **3** in DMSO-d_6. A feature of the methylamino proton signal clearly changed with a rise in temperature. The doublet of the methyl proton signal changed to a singlet via a broad doublet with a rise in temperature. On the other hand, a doublet of the amino proton signal changed to a broad one at 60 °C and almost disappeared at 100 °C. A feature of the other amino (6-NH_2) proton signal was not changed even at 100 °C. The behavior of these signals was similar to those of the corresponding proton signals of the product **5**. However, the ^1H NMR spectrum of the product **3** dramatically changed at 130 °C. The broad signal of the amino (6-NH_2) proton at 100 °C changed to a very broad one at 130 °C. At the same time, the singlet of the aromatic (C-5) proton

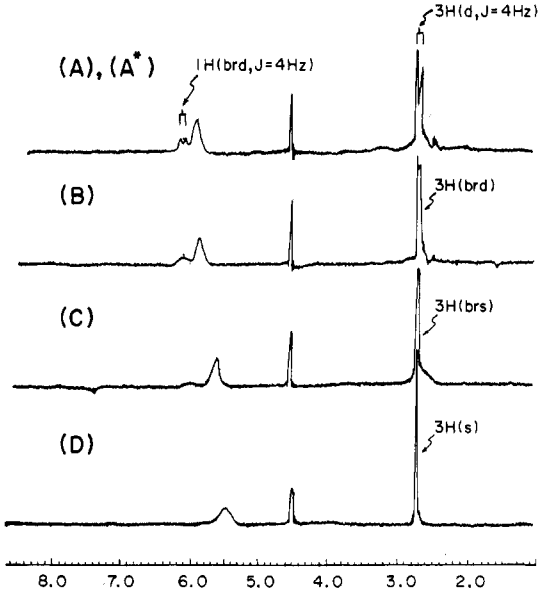


Figure 6. Temperature-dependent ^1H NMR spectra of the product **3**: (A) 35 °C; (A*) regenerated spectrum by cooling; (B) 60 °C; (C) 100 °C; (D) 130 °C.

signal also changed to a broad one. Further, a broad singlet of the amido (N-3) proton signal changed to a very broad one at 130 °C. These findings can be explained by two mechanisms. An amino–imino tautomerization similar to that of the product **5** is probably involved in the tautomerization of the product **3** in the range of 35 to 100 °C. The equilibrium between the two tautomeric forms **3a** and **3b** lies to the imino tautomer (structure **3b**) side with a rise in temperature. On the other hand, another mechanism involved in the tautomerization of the product **3** at over 100 °C is a migration of the amino (6-NH_2) and the aromatic (C_5-H) protons. The latter type of tautomerization more easily took place on the product **4** freed from a methyl substituent rather than the product **3**. The feature of the amino (2-NH_2 and 6-NH_2), aromatic (C-5), and amido (N-3) proton signals of the product **4** at 100 °C was similar to those of the corresponding proton signals of the product **3** at 130 °C (Figure 6). This finding indicates that the thermal tautomerization of the aminopyrimidine derivative **4** takes place by migration of the protons on all the nitrogen atoms at 2-, 3-, and 6-positions, in addition to the aromatic proton. Since a similar tautomerization was not observed on the 2-(methylamino)pyrimidine derivative **3** in the range of 35 to 100 °C, a methyl substituent on the nitrogen atom at the 2-position is likely to disturb the migration of the amino protons at the 6-position and the aromatic proton at the 5-position. On the other hand, the thermal tautomerization of the 1-methylpyrimidine derivatives **2a** and **2b** clearly differed from that of the other pyrimidine derivatives **3**, **4**, and **5** as described above.

A feature of the amino proton signals at the 2- and 6-positions of the product **2a** and the isomer **2b** clearly changed at higher temperature. The broad singlet of the amino proton signals of **2a** changed to a very broad one at 60 °C and almost disappeared at 100 °C. A similar change was also observed with the isomer **2b**. Both the spectra of the product **2a** and the isomer **2b** were not changed at over 100 °C. These findings suggest that the thermal tautomerization of the 1-methylpyrimidine derivatives **2a** and **2b** take place by a migration of the protons on the nitrogen atoms at the 2- and 6-positions.

Consequently, the mechanisms for the thermal tautomerization of the pyrimidine derivatives **2a**, **2b**, **3**, **4**, and **5** could be differentiated into the following three types: (a) migration of the proton between the two nitrogen atoms at the 2- and 3-positions; (b) migration of the protons on all the nitrogen atoms at the 2-, 3-, and 6-positions and the aromatic proton at 5-position; (c) migration of the protons on the nitrogen atoms at the 2- and 6-positions. Type (a) involves the thermal tautomerization of the products **3** and **5** in the range of 35 to 100 °C. Type (b) involves the thermal tautomerization of the product **3** in the range of 100 to 130 °C and the product **4** in the range of 35 to 100 °C. Type (c) involves the thermal tautomerization of the products **2a** and **2b** in the range of 35 to 100 °C. These results suggest that the methyl substituent on the nitrogen atom at the 2-position is likely to disturb the migration of the amino (6-NH_2) protons, while the methyl substituent on the nitrogen atoms at the 1-position disturb the migration of the aromatic proton at the 5-position. Also, these methyl substituents probably contribute to the stabilization of the normally disfavored imino tautomeric structure **5b** of the compound **5** in DMSO-d_6–$CDCl_3$ solution at 35 °C, since this similar tautomeric structure was not observed on the other pyrimidine derivatives under the corresponding conditions.

Table V. Yields of the Products Resulting from the Reaction of 2a with Alkylamine in the Presence of Sodium Methoxide

entry	mole ratio 2a:MeO-Na:RNH_2		yield, % 3	5	4
1	1:3		19–25		tr[a]
2	1:3:0.1	(R = Me)	19–25		tr
3	1:3:1	(R = Me)	25–41	0.5–2	tr
4	1:3:2	(R = Me)	33–53	1–3	tr
5	1:3:1	(R = Et)	19–25		tr

[a] tr = trace amount.

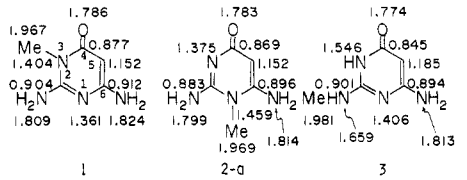


Figure 7. Electron densities on all the atoms of the monomethylpyrimidine derivatives **1**, **2a**, and **3**.

Mechanisms for the Formation of the Products 4 and 5. The formation of the two unexpected side products **4** and **5** was found in the condensation of ethyl cyanoacetate with methylguanidine as described above. The product **5** has not been reported yet as a natural product or a synthetic material. The mechanism for the formation of both these compounds **4** and **5** was investigated. Since methylamine is a probable source for the additional methyl group of the compound **5**, several reactions of the hemisulfate of the compound **2a** with methylamine were performed under various conditions as given in Table X. The results are given in Table V. The yields of the products were determined on the basis of each standard curve on HPLC. The reaction of **2a** with the equimolar amount of methylamine gave the compound **5** in extremely low yield (0.5–2%) in addition to the compound **3** as a major product (19–53% yield); this compound probably results from a Dimroth-type rearrangement[6,7] on **2a** with sodium methoxide. However, the yield of **3** was only 20% when **2a** was treated with a sodium methoxide solution freed from methylamine. When **2a** was treated with the twice molar amount of methylamine, on the other hand, the formation of the compound **3** rose up to a yield of 50%. These facts indicate that methylamine has a catalytic ability to cause

Table VI. Yields of the Products Resulting from the Reacton of 2a with Guanidine Derivatives

entry	mole ratio 2a:MeONa: RHNC(=NH)NH$_2$		yield, % 3	4
1	1:3		19–25	tr[a]
2	1:3:1	(R = Me)	22–33	tr
3	1:3:2	(R = Me)	27–32	tr
4	1:3:1	(R = H)	13–32	10–11
5	1:3:2	(R = H)	34–45	17–28

[a] tr = trace amount.

the Dimroth-type rearrangement for **2a**.

The electron-attracting ability of **2a** was evaluated by Hückel MO calculations on the monomethylpyrimidine derivatives **1**, **2a**, and **3**. Figure 7 shows electron densities of all the atoms of these compounds. When the electron density on C-2 of the pyrimidine nuclei was compared with those of compounds **1**, **2a**, and **3**, the lowest electron density on C-2 of **2a** was observed, indicating the highest electron-attracting ability of this carbon. Thus, it was found that **2a** has a tendency to favor the amine exchange reaction at the C-2 with methylamine.

Another reaction, such as the amine exchange reaction on **3** with methylamine, was expected for the formation of **5**. Therefore, **3** was treated with methylamine in a manner similar to that for the reactions of **2a** with methylamine. No reaction, however, occurred under these conditions.

The reactions of **2a** with alcoholic methylamine afforded **5** in low yield. This result led us to survey in detail the fused products of methylamine hydrochloride with dicyanodiamide. Mass spectral analysis of the products indicated the formation of methylguanidine as a major product and the concomitant formation of two minor side products such as guanidine and dimethylguanidine. Therefore, the methylguanidine was expected to be the methyl source for the formation of **5**. The hemisulfate of **2a** was treated with methylguanidine under conditions (Table XI) similar to those for the reactions of **2a** with methylamine. As shown in Table VI, these reactions gave only the compound **3** in low yield (22–33%). Further, the hemisulfate of **2a** was treated with guanidine. This reaction gave **4** (10–28%) and **3** (13–45%) (Table VI). The yield of **3** rose to 45% by addition of the twice molar amount of guanidine. However, the compound **5** was not produced under these conditions. The formation of **4** is probably due to a Watanabe-type N_1–C_2–N_3 replacement[5] on **2a** with guanidine.

Consequently, the reaction of **2a** with methylamine or guanidine derivatives in the presence of sodium methoxide was found to give three products, **3**, **4**, and **5**. The major product **3** probably arises from **2a** by a Dimroth-type rearrangement catalyzed with both methylamine and guanidine. The minor product **4** probably arises from a Watanabe-type replacement on **2a** with guanidine. However, the yield of the product **4** from this reaction was lower than that of the same product on the reaction of ethyl cyanoacetate with methylguanidine as described above. Further, an amine exchange reaction of **2a** with methylamine gave extremely low yield of **5**. On the other hand, both guanidine and dimethylguanidine were identified as side products in the preparation of methylguanidine. This finding suggests that the N_1–C_2–N_3 moieties of the compounds **4** and **5** are likely to originate from the guanidine and dimethylguanidine, respectively. The reaction of ethyl cyanoacetate with the fully purified methylguanidine was therefore carried out under conditions similar to those reported in the literature,[2-4] and it was found that the reaction afforded **2a** (31%) and **3** (3%), but did not yield compounds **4** and **5**. Accordingly, the formation of the side products **4** and **5** was most probably caused by reaction of ethyl cyanoacetate with guanidine and dimethylguanidine, respectively, which were concomitantly formed in the preparation of methylguanidine. However, a Watanabe-type replacement on **2a** with guanidine could not be neglected as an alternative mechanism for the formation of **4**.

Experimental Section

General. UV spectra were obtained on a Shimadzu UV-240 spectrometer and recorded in ethanol or distilled water. Infrared spectra were obtained on a JASCO IRA-1H. ^{1}H NMR spectra was obtained on a Hitachi R-22 spectrometer by use of TMS as internal standard and recorded in DMSO-d_6, DMSO-d_6–$CDCl_3$, or D_2O. ^{13}C NMR spectra were obtained on a Hitachi R-42FT NMR spectrometer by use of TMS or [1-^{13}C]acetate as internal standard and recorded in DMSO-d_6, DMSO-d_6–D_2O, or 2.8% NH_4OH in D_2O. Mass spectra were obtained on a Shimadzu QP-1000 mass spectrometer and recorded by the direct inlet method at 70 eV. High resolution mass spectra were obtained on a Hitachi RMU-6L mass spectrometer at 70 eV. High performance liquid chromatography (HPLC) was performed on Radial Pak 8s105 (silica gel) with $CHCl_3$–2.8% NH_4OH in methanol (3:2 v/v) as the mobile phase. The flow rate was 2.0 mL/min and the absorption was measured at 254 nm.

Reaction of Ethyl Cyanoacetate with Methylguanidine. Following the method reported in ref 2, a mixture of methylamine hydrochloride (9.9 g) and dicyanodiamide (6.2 g) was fused and then the fused material was dissolved in methanol (60 mL). To this solution were added ethyl cyanoacetate (12.8 g) and sodium methoxide (14.4 g) slowly. The mixture was refluxed for 4 h, filtered, and neutralized with dilute hydrochloric acid to yield a precipitate (13.2 g). The precipitate, after filtration, was recrystallized twice from 400 mL of hot water to give 3.4 g of product **2a** (97% pure on HPLC) as a white amorphous powder. The filtrate was evaporated in vacuo to give a brown cake (14.4 g). The cake was subjected to column chromatography on silica gel with methanol as eluent. Following elution of a mixture (9.6 g) of the products **3**, **4**, and **5**, isomer **2b** was eluted. The mixture (9.6 g) was again subjected to column chromatography on silica gel with a $CHCl_3$/2.8% methanol solution of ammonia (1:2–2:3) as eluent to give three products: **3** (0.4 g), **4** (3.3 g), and **5** (0.4 g). When the reaction was repeated at threefold larger scale under the same conditions as above, yields of the products were in the range shown in parentheses: **2a** (33–35%), **3** (4–6%), **4** (27–35%), **5** (3–4%), and **2b** (2–4%). When a mixture of $CHCl_3$ and 2.8% methanol solution of ammonia was used as eluent in place of methanol for column chromatography of the cake described above, on the other hand, isomer **2b** was not given, but the product **2a** was given in place of **2b**. The physical data of the products **2a** and **3** were identical with the reported data.[2-4]

2,6-Diamino-1-methyl-4(1*H*)-pyrimidinone (2a): mp 275–280 °C dec; UV (H_2O, pH 6.91) 266 nm (ϵ 13 590); IR (Nujol) 3347 (NH), 3139 (NH_2), 1657 (CON), 1565, 1509, and 1489 cm^{-1} (pyrimidine C=C); mass spectrum, m/z (rel intensity) 140 (M^+, 100), 126 (10), 113 (23), 100 (53), 98 (30), 82 (41), 68 (34), 57 (66), 44 (97), 43 (92), 42 (59), 41 (77); high resolution mass spectrum, found m/z 140.0693, calcd for $C_5H_8N_4O$ M, 140.0697.

Hemisulfate of the Product 2a. Following the method in literature,[2] sulfuric acid was added to pH 2 to the product **2a** (2.4 g) suspended in 170 mL of water at 50 °C. The solution, after addition of Darco G-60, was filtered, and the filtrate was cooled overnight to give 1.0 g of the hemisulfate as colorless needles. Anal. Calcd for $C_5H_8N_4O \cdot {}^1/_2H_2SO_4 \cdot H_2O$: C, 28.98; H, 5.35; N, 27.04. Found: C, 29.00; H, 5.21; N, 27.18.

Crystallographic Measurement. The crystallographic analysis of the hemisulfate was performed on a Syntex R3 diffractometer with graphite-monochromated Mo Kα radiation. Cell dimensions were derived by the least-squares method from setting angles of 21 well-centered diffraction peak. A total of 1367 reflections were collected by ω-scan ($2\theta_{max}$ = 58.0°) and 1031 reflections having $I_0 > 1.96\sigma(I_0)$ were used for the structure determination.

Table IX. Assignment of the ^{1}H NMR (DMSO-d_6) Spectral Signals for the Pyrimidine Derivatives

compd	1-NMe	2-NHMe	N(3)H	H-5	NH_2
2a	3.31 (3.48)[a]			4.91 (5.36)[a]	6.98, 7.09
2b	3.18 (3.31)[a]		10.0[b]	4.60	6.18, 6.67 (NH)
3		2.73, 6.09 (2.90)[a]	9.76	4.47	5.91
4			9.71	4.47	5.87, 6.16
5	3.17 (3.42)[a]	2.70, 6.66 (2.98)[a]		4.63	6.03

[a] Recorded in D_2O. [b] Very broad signal.

Crystal data of the hemisulfate: $C_5H_8N_4O\cdot{}^1/_2H_2SO_4\cdot H_2O$, M_r = 207.21; crystal dimensions 0.45 mm × 0.50 mm × 2.00 mm; orthorhombic, space group *Pcan*, a = 7.608 (3), b = 14.611 (8), and c = 15.506 (8) Å, U = 1723.7 Å^3, D_c = 1.66 g/cm^3, Z = 8, D_m = 1.65 g/cm^3, μ(Mo Kα) = 0.8 cm^{-1}.

Structure Analysis and Refinement. The phases of 127 reflections with $|E| > 1.60$ were determined by direct methods with MULTAN.[11] The E map for the best solution yielded positions for all atoms except hydrogens. Anisotropic refinement for carbon, nitrogen, sulfur, and oxygen atoms by full-matrix least-square calculations reduced the final R index to 0.081. Final atomic coordinates, bond lengths, and bond angles are given in Tables VII and VIII (supplementary material).

6-Amino-2-(methylamino)-4(3*H*)-pyrimidinone (3). Recrystallization from a mixture of methanol and distilled water (2:1) gave 0.2 g of **3** as white crystals: mp 232–234 °C; UV (EtOH) 272 (ε 16 280) and 218 (15 790); IR (Nujol) 3450, 3360 (NH), 3240 (NH_2), 1660 (CON), and 1500 cm^{-1} (pyrimidine C=C); mass spectrum, m/z (rel intensity) 140 (M$^+$, 100), 112 (21), 111 (42), 95 (26), 85 (20), 67 (10), 57 (45), 43 (32), 42 (24), 41 (24). Anal. Calcd for $C_5H_8N_4O\cdot H_2O$: C, 37.97; H, 6.37; N, 35.43. Found: C, 37.73; H, 6.50; N, 35.18.

2,6-Diamino-4(3*H*)-pyrimidinone (4). Recrystallization from a mixture of methanol and distilled water (2:1) gave 1.8 g of **4** as white crystals: mp 267–269 °C; UV (EtOH) 270 (ε 11 060), and 214 (16 410); IR (Nujol) 3350 (NH), 3230 (NH_2), 3150 (CH), and 1650 cm^{-1} (CON); mass spectrum, m/z (rel intensity) 126 (M$^+$, 63), 98 (23), 73 (13), 68 (23), 60 (35), 57 (23), 55 (23), 45 (31), 44 (25), 43 (100). Anal. Calcd for $C_4H_6N_4O\cdot H_2O$: C, 33.33; H, 5.60; N, 38.89. Found; C, 33.27; H, 5.70; N, 38.62.

6-Amino-1-methyl-2-(methylamino)-4(1*H*)-pyrimidinone (5a) or 6-Amino-1-methyl-2-(methylimino)-1,2-dihydro-4-(3*H*)-pyrimidinone (5b). Recrystallization from a mixture of methanol and distilled water (2:1) gave 0.3 g of **5** as yellow crystals: mp 281–282.5 °C; UV (EtOH) 268 (ε 15 970) and 216 (22 210); IR (Nujol) 3500 (NH), 3260–3150 (NH_2, CH), 1676, 1628 (CON), 1590, 1540, and 1500 cm^{-1} (pyrimidine C=C); mass spectrum, m/z (rel intensity) 154 (M$^+$, 87), 139 (9), 82 (79), 57 (100). Anal. Calcd for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 43.38; H, 6.68; N, 36.06.

Isomer 2b of 2a. Recrystallization from a mixture of methanol and distilled water (3:2) gave 0.05 g of **2b** as colorless crystals: mp 233–235 °C; UV (EtOH) 266 (ε 14 970) and 216 (17 320); IR (Nujol) 3335 (NH), 3207 (NH_2), 3111 (CH), 1669 (CON), 1645, 1613, 1573, 1513, and 1485 cm^{-1} (pyrimidine C=C); mass spectrum, m/z (rel intensity) 140 (M$^+$, 100), 111 (24), 100 (68), 98 (19), 83 (35), 82 (21), 70 (35), 68 (35), 57 (65), 55 (53), 45 (24), 43 (71), 42 (32), 41 (59). Anal. Calcd for $C_5H_8N_4O\cdot H_2O$: C, 37.97; H, 6.37; N, 35.43. Found: C, 37.96; H, 6.44; N, 35.83.

Hemisulfate of 2b. Anal. Calcd for $C_5H_8N_4O\cdot{}^1/_2H_2SO_4\cdot H_2O$: C, 28.98; H, 5.35; N, 27.04. Found: C, 28.96; H, 5.37; N, 26.74. Crystal data for this hemisulfate completely coincided with those of the hemisulfate of **2a** described above.

Table IX shows the assignment of the ^{1}H NMR signals of the compounds **2a**, **2b**, **3**, **4**, and **5**.

Acetylation of Product 5. The product **5** (40 mg) was acetylated with a mixture of dry pyridine (0.5 mL) and acetic anhydride (0.5 mL) to give only monoacetate **6** (30 mg).

6-Acetamido-1-methyl-2-(methylamino)-4(1*H*)-pyrimidinone (6a) or 6-Acetamido-1-methyl-2-(methylimino)-1,2-dihydro-4(3*H*)-pyrimidinone (6b): mp 247–250 °C; IR (Nujol) 3523, 3248, 3203 (NH and CH), 1701 (NH*C*O*C*H$_3$), 1641 (CON), 1601, and 1536 cm^{-1} (pyrimidine C=C); mass spectrum, m/z (rel intensity) 196 (M$^+$, 16), 181 (27), 154 (3), 37 (100); ^{1}H NMR (DMSO-d_6) δ 2.04 (3 H, s, CO*Me*), 2.76 (3 H, d, J = 4 Hz, NH*Me*), 5.42 (1 H, s, H-5), 7.00 (1 H, d, J = 4 Hz, N*H*Me), 9.89 (2 H, br s, N*H*CO × 2); ^{13}C NMR (DMSO-d_6) δ 170.2 (CO), 169.5 (C-4), 154.8 (C-2), 145.2 (C-6), 99.3 (C-5), 32.0 (Me), 28.4 (Me), 23.0 (Me).

Table X. Molarities (mmol) of the Hemisulfate, RNH_2, and NaOMe in the Reaction of 2a with Alkylamine

entry	hemisulfate	RNH_2	NaOMe
1	0.43		1.29
2	0.43	0.04 (R = Me)	1.29
3	0.43	0.43 (R = Me)	1.72
4	0.43	0.86 (R = Me)	2.15
5	0.43	0.43 (R = Et)	1.72

Table XI. Molarities (mmol) of the Hemisulfate, Guanidine Derivatives, and Sodium Methoxide in the Reactions of 2a with Guanidine and Guanidine Derivatives

entry	hemisulfate	RNHC(=NH)NH_2	NaOMe
1	0.43		1.29
2	0.43	0.43 (R = Me)	1.72
3	0.43	0.86 (R = Me)	2.15
4	0.43	0.43 (R = H)	1.72
5	0.43	0.86 (R = H)	2.15

Standard Curves for 3, 4, and 5. The standard curves for **3**, **4**, and **5** were obtained by using a line regression analysis by the method of least squares via HPLC.

Reaction of 2a with Methylamine. To a solution of the hemisulfate (100 mg) of **2a** in methanol (2 mL) was added methylamine hydrochloride (56 mg) dissolved in a 28% methanol solution (0.3 mL) of sodium methoxide. This mixture was refluxed for 24 h. In a similar manner, the other four reactions (entry 2 to 5) were performed under various conditions as given in Table X. Each reaction was repeated three times under same conditions. All the compounds were separated by HPLC to elucidate their structures by comparison of the spectra. The yields of the products were obtained from the standard curves.

Reaction of 3 with Methylamine. To a solution of **3** (50 mg) in methanol (2 mL) was added methylamine hydrochloride (21 mg) dissolved in a 28% methanol solution (0.1 mL) of sodium methoxide. The mixture was refluxed for 24 h. However, no product was found on HPLC.

Identification of Methylguanidine. A mixture of methylamine hydrochloride (28.4 mg, 0.43 mmol) and dicyanodiamide (36.2 mg, 0.43 mmol) were fused at 180 °C for 3.5 h. This fused material was analyzed by means of mass spectral measurements. A major product and two minor products were detected and assigned to methylguanidine [mass spectrum, m/z (rel intensity) 73 (M$^+$, 100) and 59 (94)], guanidine [m/z 59 (M$^+$, 100)], and dimethylguanidine [m/z 87 (M$^+$, 47), 73 (100), 58 (3)], respectively, on the basis of those mass fragmentation patterns.

Reaction of 2a with Methylguanidine or Guanidine. To a methanol solution (2 mL) of either methylguanidine hydrochloride (31 mg, 0.43 mmol, Sigma Co. Ltd.) or guanidine hydrochloride (25 mg, 0.43 mmol, Wako Pure Chemical Industries Ltd.) was added the hemisulfate (100 mg, 0.43 mmol) of **2a** dissolved in a 28% methanol solution (0.3 mL) of sodium methoxide. The mixture was refluxed for 24 h. Each reaction was repeated three times under same condition. The yields of the products were determined in the same manner as that for the reaction of **2a** with methylamine. In a similar manner, the other

reactions were performed under various conditions as given in Table XI.

Reaction of Ethyl Cyanoacetate with Purified Methylguanidine. Mass spectral analysis of the commercial methylguanidine hydrochloride described above showed that the sets of peaks originated from only methylguanidine but did not the peaks for guanidine and dimethylguanidine as contaminants. Therefore, this commercial one was used for the following reaction. To a methanol solution (6 mL) of methylguanidine hydrochloride (100 mg, 0.91 mmol) were added ethyl cyanoacetate (69 mg, 0.61 mmol) and sodium methoxide (90 mg, 1.64 mmol). The mixture was refluxed for 4 h. The yields of the products of this reaction were determined in the same manner as described above.

Acknowledgment. We are deeply indebted to Dr. Toshifumi Hirata of the Department of Chemistry, Faculty of Science, Hiroshima University, for his assistance with the X-ray crystallography.

Registry No. **2a**, 51093-34-6; **2a**·$^1/_2H_2SO_4$·H_2O, 111291-91-9; **2b**, 111291-90-8; **2b**·$^1/_2H_2SO_4$·H_2O, 111291-93-1; **3**, 89181-81-7; **4**, 56-06-4; **5a**, 111291-89-5; **5b**, 111323-81-0; **6a**, 111291-94-2; **6b**, 111291-95-3; $NCCH_2CO_2CH_2Me$, 105-56-6; $MeNHC(=NH)NH_2$, 471-29-4; $MeNH_2$.HCl, 593-51-1; $H_2NC(=NH)NHCN$, 461-58-5; $H_2NC(=NH)NH_2$, 113-00-8; $Me_2NC(=NH)NH_2$, 3324-71-8.

Supplementary Material Available: Tables VII and VIII, atomic coordinates and bond lengths and angles for **2a** hemisulfate (3 pages). Ordering information is given on any current masthead page.

Conformational Effects on the Oxidative Coupling of Benzyltetrahydroisoquinolines to Morphinane and Aporphine Alkaloids

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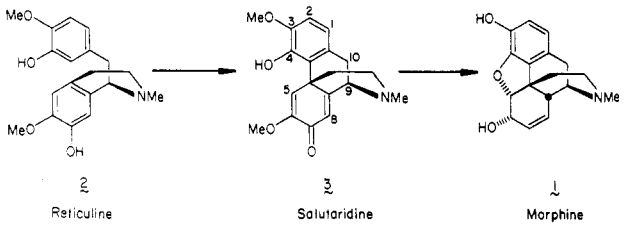
Conformationally rigid 1-benzyltetrahydroisoquinolines **7a** and **7b** were prepared. Oxidation of **7a** with vanadium oxychloride or thallium(III) trifluoroacetate gave structures related to aporphine alkaloids as did oxidation of **7b** with vanadium oxyfluoride. Oxidation of **7a** with (diacetoxyiodo)benzene gave a mixture of structures related to aporphine and morphinane alkaloids.

A great deal of effort has been expended toward developing laboratory syntheses of the alkaloid morphine **1**. Much of this effort has focused on mimicry of the biosynthetic pathway, in particular on the key step in the biosynthesis, the oxidative phenolic coupling of reticuline **2** to salutaridine **3** (Scheme I).[1,2] This oxidative coupling step can, in principle, give salutaridine (**3**), isosalutaridine (**4**), isoboldine (**5**), and corytuberine (**6**) (Figure 1). Reticuline or *N*-acyl-*N*-norreticuline derivatives have been treated with a variety of oxidants to achieve a wide range of yields of these four possible products.[3-6] Several theories have been offered to explain the regiochemical outcome of these studies, including coordination effects,[1b] anion effects,[3b] and steric interactions.[3d] The purpose of this study was to examine conformational effects that may influence the partitioning of benzyltetrahydroisoquinolines between morphinanes and aporphines upon oxidation.

If one examines molecular models, it is evident that reticuline can adopt two conformations, one in which the benzyl side chain is equatorially disposed (**2e**) or one in which it is axially disposed (**2a**) (Scheme II). Conformer **2e** can only lead to aporphines, whereas conformer **2a** can afford both aporphines and morphinanes. Spectroscopic evidence for the conformational equilibrium of benzyltetrahydroisoquinolines has been presented by Cava and Fraenkel.[7] Given that this conformational equilibrium may well be in effect, it was the purpose of this study to determine whether the conformation of reticuline controls the eventual product distribution.[8] Specifically, does conformation **2a** in which the benzyl group is axially disposed lead to morphinanes only, or both morphinanes and aporphines? To answer this question, we decided to prepare compounds **7a**, **7b**, and **11c** in which the benzyl group is axially disposed, and examine their behavior in oxidative phenolic coupling reactions.[9]

Scheme I



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