A NEW APPROACH TO FUSED 1,2-DIAZEPINES BY CYCLIZATION OF ENHYDRAZINES WITH α- AND β-KETO ESTERS

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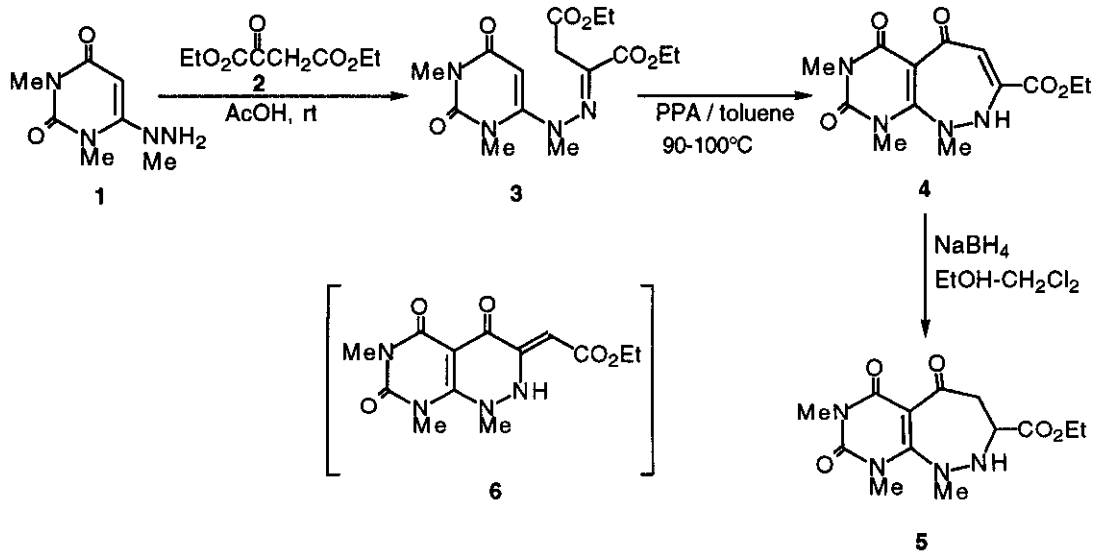
Abstract - The cyclization of 6-(1,2-diethoxycarbonylethylidene)hydrazino-1,3-dimethyluracil (**3**) and 6-(1,2-diethoxycarbonylethylidene)hydrazino-3-methyl-2-methylthiopyrimidin-4(3*H*)-one (**8**) in the presence of polyphosphoric acid (PPA) provided 2,5-dihydropyrimido[4,5-*c*]-1,2-diazepine-5,6,8(1*H*,7*H*,9*H*)-trione (**4**) and 4,5-dihydropyrimido[4,5-*c*]-1,2-diazepine-5,6(1*H*,7*H*)-dione (**9**), respectively. 4-Hydrazino-5-methyl-2-pyrone (**27**) and 5,5-dimethyl-3-hydrazino-cyclohexen-1-one (**31**) readily reacted with ethyl benzoylacetate (**28**) to give 4,5-dihydropyrano[4,3-*c*]-1,2-diazepine-5,6(1*H*,7*H*)-dione (**30**) and 3-phenyl-1,8,8-trimethyl-4,5,6,7,8,9-hexahydro-1,2-benzodiazepine-5,6(1*H*)-dione (**33**), respectively.

Enhydrazines are synthetically interesting compounds because they exhibit versatility in the preparation of nitrogen-containing heterocycles to produce various heterocycles, pyrrole,[1-3] pyrazole,[4,5] pyridine,[1,2] pyridazine,[2,6,7] 1,2,4-triazine[8] and fused 1,2-diazepine rings.[1,6] We previously reported that heating of the Michael adducts of enhydrazines with dimethyl acetylenedicarboxylate in the presence of PPA afforded fused 5-oxo-1,2-diazepines in good yields.[1] To our knowledge, there has no report on the preparation of fused 5-oxo-1,2-diazepines by the use of enhydrazines. As a continuation of our study on a new synthesis

of 1,2-diazepines, we examined the reaction of enhydrazines with diethyl oxalacetate (**2**), diethyl oxalpropionate (**12**) and ethyl benzoylacetate (**28**).

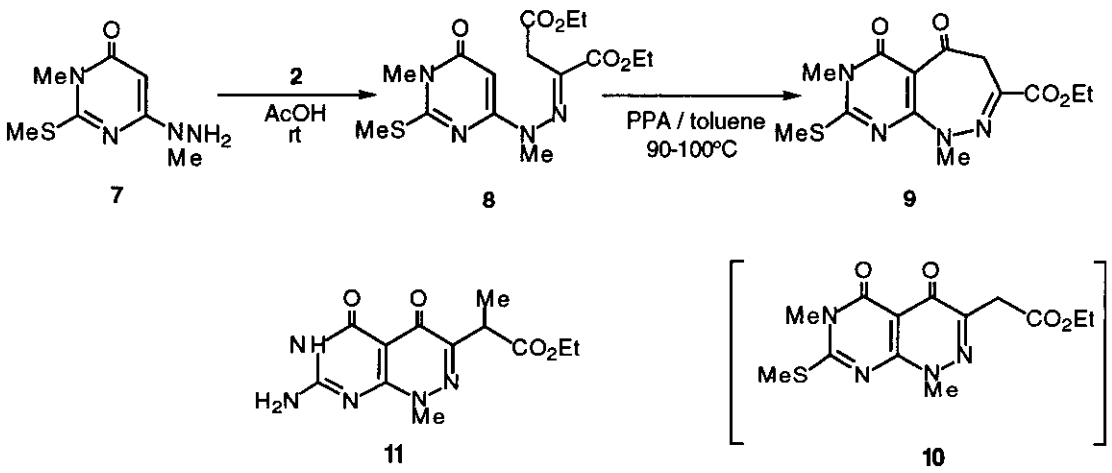


Scheme 1

When the hydrazone (**3**) prepared by the reaction of 1,3-dimethyl-6-hydrazinouracil (**1**) with diethyl oxalacetate (**2**) was heated in toluene at 90-100°C in the presence of PPA, 2,5-dihydropyrimido[4,5-*c*]-1,2-diazepine-5,6,8(1*H*,7*H*,9*H*)-trione (**4**) was expectedly provided in good yield (Scheme 1). The MS spectrum indicated the parent ion peak corresponding to the elimination of ethanol from the reactant (**3**). In the ^{1}H-NMR spectrum, the methine signal of pyrimidine ring was disappeared and the ^{13}C-NMR spectrum showed the sp^2 carbon at the C-5 of pyrimidine ring at δ 98.3. In this reaction, however, the structural isomer (**6**) is possible to form as the product by cyclization through nucleophilic attack of the negatively polarized C-5 in the pyrimidine ring on the carbonyl group of a further ester. To confirm the structure of **4**, the product (**4**) was reduced with $NaBH_4$ to give 2,3,4,5-tetrahydropyrimido[4,5-*c*]-1,2-diazepine-5,6,8(1*H*,7*H*,9*H*)-trione (**5**). The ^{1}H-NMR spectrum of **5** showed the geminal 4-H at δ 3.23, the geminal 4-H at δ 3.40, the methine 3-H at δ 4.64, respectively. Also the IR spectrum exhibited ester carbonyl and the NH absorptions at 1730 and 3415 cm^{-1}, respectively, and the absence of a hydrogen bond. These results support that the assigned structure (**4**) for the product is reasonable.

Treatment of the hydrazone (**8**) prepared by the reaction of 6-hydrazino-2-methylthiopyrimidine (**7**) with **2** under the similar conditions to the preparation of **4** produced 4,5-dihydropyrimido[4,5-*c*]-1,2-diazepine-

5,6(1*H*,7*H*)-dione (**9**) in 82 % yield (Scheme 2). The ^{1}H-NMR spectrum showed the methylene signal of diazepine ring at δ 3.67 and the ^{13}C-NMR spectrum exhibited the sp^2 carbon at the C-5 of pyrimidine ring and the methylene carbon of diazepine ring at δ 98.3 and 46.6, respectively. The IR and MS spectral data satisfied the assigned structure (**9**). However, these data cannot discriminate between **9** and another possible isomer (**10**). Therefore, the UV spectrum of the product (**9**) was compared with that of the known compound (**11**), 7-amino-1,3-dimethylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione,[7] structurally similar to **10**. The UV spectrum of **9** showed the maximum absorption peaks at 258.5 and 302.0 nm, and the spectral pattern was quite different from that of **11** (Figure). Moreover, the ^{1}H-^{13}C long-range correlation spectrum of the product exhibited a clear cross peak arising from three-bond coupling between the methylene hydrogen at δ_H 3.67 and C-5a at δ_C 102.4. These results support the assigned structure (**9**) for the product.



Scheme 2

We also examined the cyclization of hydrazinopyrimidines (**1**) and (**7**) with diethyl oxalpropionate (**12**). First, reaction of **1** with **12** was carried out in acetic acid at room temperature. However, the hydrazone (**13**) could not be isolated because of many spots on TLC. Then, after recognition of disappearance of **1** on TLC in this reaction, the reaction mixture was refluxed to give 6-ethoxycarbonyl-1,3,5,7-tetramethyl-pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**14**) and 6-ethoxycarbonyl-1,3,5-trimethylpyrrolo[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**15**) in 12 % and 29 % yields, respectively, recovering **1** in 20 % yield (Scheme 3). All ^{1}H-NMR, ^{13}C-NMR and MS spectral data were in accord with the assigned structures

(**14**) and (**15**). The reaction pathway to the pyrrolopyrimidines (**14**) and (**15**) is presumed to proceed as shown in Scheme 4. The dehydrated compound (**16**) was protonated to produce the protonated compounds (**17**) and (**20**), and then [3,3]sigmatropic rearrangement of **17** and **20** followed by nucleophilic attack of the methylamino group of **18** and the imino group of **21** on the imino carbon and C-6, respectively, to afford **14** and **15**.

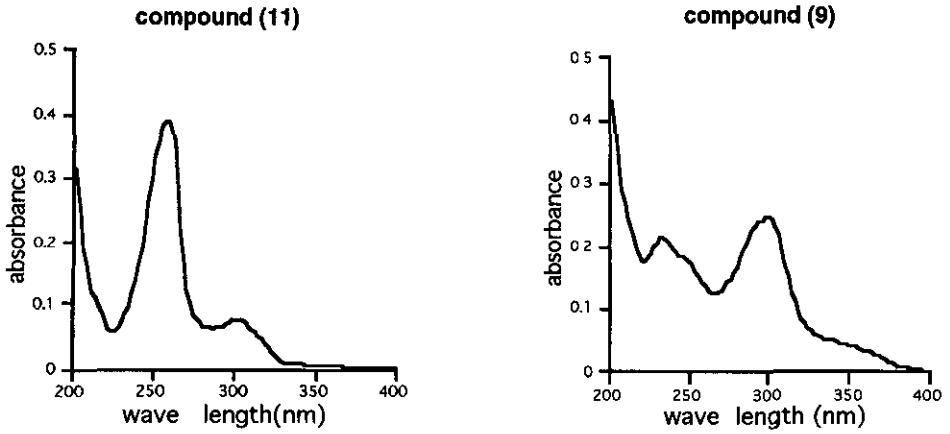
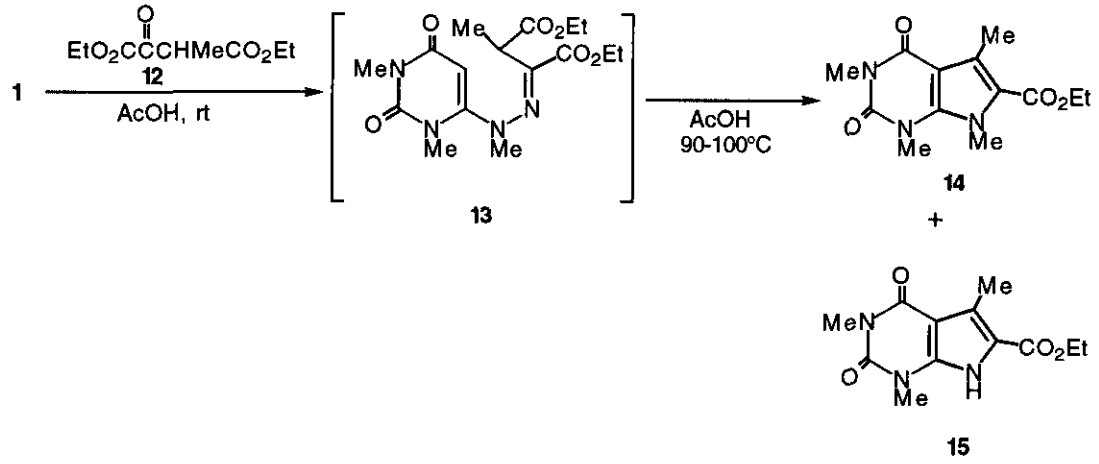
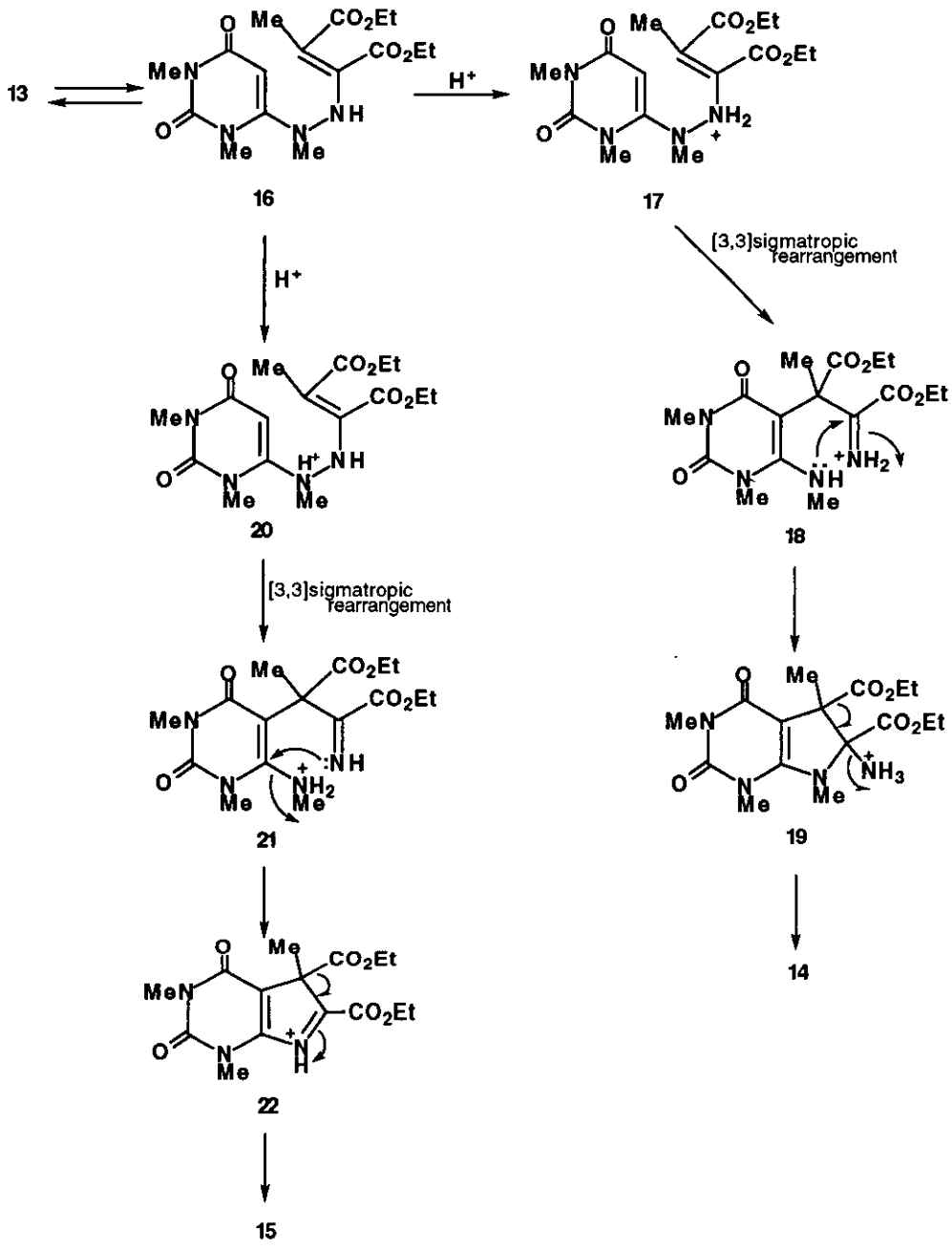


Figure UV spectra of 7-amino-1,3-dimethylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione (11) and 4,5-dihydropyrimido[4,5-*c*]-1,2-diazepine-5,6(1*H*,7*H*)-dione (9)



Scheme 3

The cyclization of **7** with **12** under the similar conditions to the reaction of **1** with **12** gave 6-ethoxycarbonyl-2-methylthio-3,5,7-trimethylpyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**24**) and 1,6-dimethyl-7-methylthiopyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione (**25**) in low yields (Scheme 5). As to the structure of the product (**25**), the isomer (**26**) is also possible. In order to discriminate the structure (**25**) and (**26**),

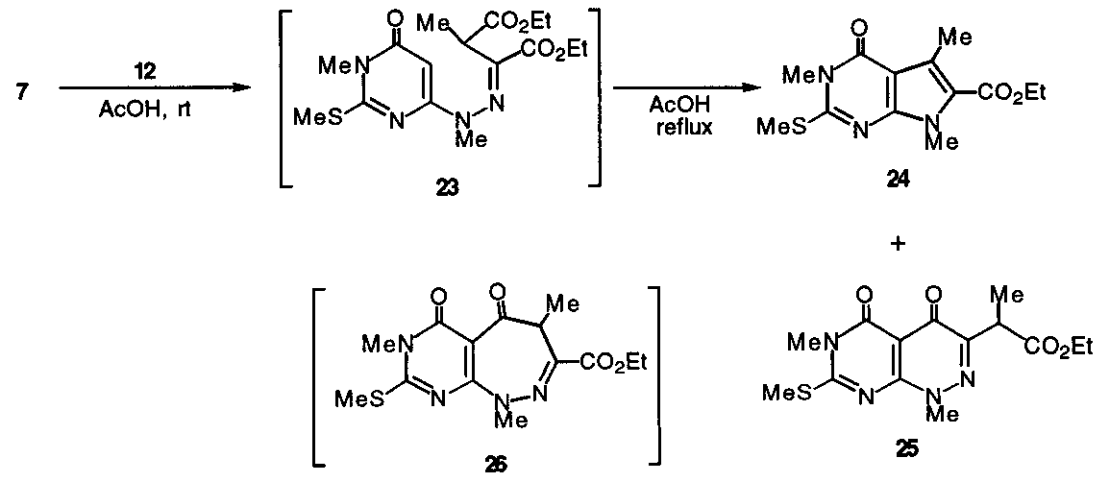


Scheme 4

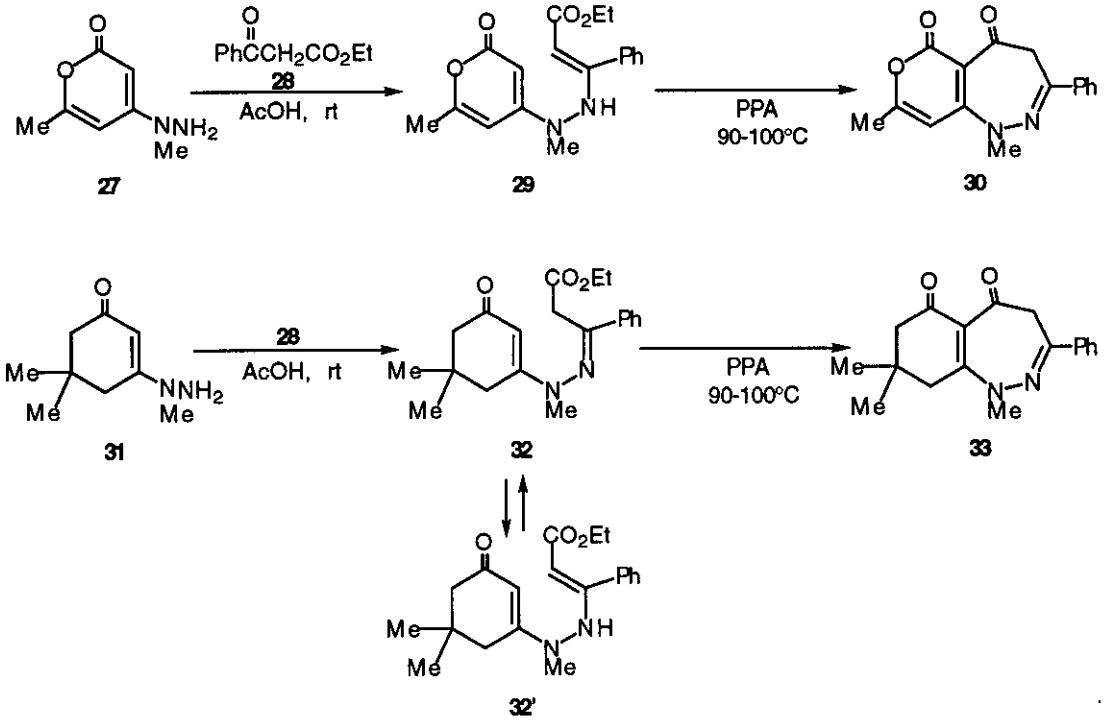
the UV spectrum of **25** was compared with that of the prepared compound (**9**), structurally similar to **26**, and they showed a quite different spectral pattern. From this result, the structure of the product is evident to be **25**.

Furthermore, we tried to prepare the fused 1,2-diazepines by the cyclization of enhydrazines with ethyl

benzoylacetate (**28**) in the presence of PPA. When the 4-(1-methyl-2-vinylhydrazino)-2-pyrone (**29**) easily prepared by the reaction of the 4-hydrazino-6-methyl-2-pyrone (**27**) with **28** was heated in PPA at 90-100°C, 4,5-dihydropyrano[4,3-*c*]-1,2-diazepine-5,6(1*H*,7*H*)-dione (**30**) was obtained in 84% as the sole



Scheme 5



Scheme 6

product (Scheme 6). We also tried the cyclization of **29** under basic conditions in the presence of triethylamine and sodium ethoxide, but the fused 1,2-diazepine was not isolated. In reaction of the hydrazinocyclohexenone (**31**) with **28** in acetic acid, an oily equilibrium mixture of the hydrazone form **32** and the enhydrazine form **32'** was isolated in 65 % yield. Heating of the oily compound in PPA successfully produced 3-phenyl-1,8,8-trimethyl-4,5,6,7,8,9-hexahydro-1,2-benzodiazepine-5,6(1*H*)-dione (**33**) in 63 % yield (Scheme 6).

Another novel synthetic approach to fused 1,2-diazepines from enhydrazine compounds is currently under investigation.

EXPERIMENTAL

All the melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded with a JASCO IRA-1 grating IR spectrophotometer. UV spectra were measured on a SHIMADZU UV-1600 spectrophotometer in methanol and expressed as λ_{max} nm (log ε). JEOL JNM-EX-270 and GX 400 spectrometers were used for both ^{1}H- (270 and 400 MHz) and ^{13}C-NMR (67.5 and 100 MHz) spectra. MS spectra were obtained with a JEOL JMS-DX 303 mass spectrometer.

6-(1,2-Diethoxycarbonylethylidene)hydrazino-1,3-dimethyluracil (3)

To a solution of **1** (10 mmol, 1.84 g) in acetic acid (20 mL) was added diethyl oxalacetate sodium salt (15 mmol, 3.15 g) and the mixture was stirred for 12 h at rt. After evaporation of the solvent under reduced pressure below 30 °C, water (300 mL) was added to the residue and the solvent was extracted with CH_2Cl_2 (100 mL x 3). The organic layer was evaporated and then the residue was purified by a silica gel column chromatography ($CHCl_3$: MeOH = 25 : 1) to give **3** (2.87 g, 81 %). The analytical sample was purified by recrystallization from CH_2Cl_2-isopropyl ether. mp 121 °C; IR (KBr) ν 1730, 1710, 1700 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.24 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 1.37 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 3.17 (3H, s, NCH_3), 3.34 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 3.61 (2H, s, CH_2), 4.14 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 4.36 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 5.54 (1H, s, CH=); ^{13}C-NMR ($CDCl_3$, TMS) δ 14.3 (CH_3), 14.5 (CH_3), 28.4 (CH_3), 32.8 (CH_3), 35.7 (CH_2), 44.8 (CH_3), 62.2 (CH_2), 63.0 (CH_2), 91.8 (CH=), 151.1 (C), 152.6 (C), 158.1 (C), 163.0 (C), 163.7 (C), 167.4 (C); MS(EI): m/z 354 (M^+); *Anal.* Calcd for $C_{15}H_{22}N_4O_6$: C, 50.84; H, 6.26; N, 15.81. Found: C, 50.60; H, 6.15; N, 16.08.

2,5-Dihydropyrimido[4,5-*c*]-1,2-diazepine-5,6,8(1*H*,7*H*,9*H*)-trione (4)

To PPA (4.06 g) at 90-100 °C was added dropwise a solution of **3** (3 mmol, 1.06 g) in toluene (20 mL) and the reaction mixture was kept at 90-100 °C. After being stirred for an additional 30 min at 90-100 °C, the toluene layer was decanted from the reaction mixture, and the oily residue was diluted with water (100 mL) while being stirred. The resulting crystals were filtered off and recrystallized from acetonitrile to give **4** (0.76 g, 82 %). mp 217 °C; IR (KBr) ν 1710, 1700, 1665 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.38 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 3.36 (3H, s, NCH_3), 3.77 (3H, s, NCH_3), 4.15 (3H, s, NCH_3), 4.35 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 6.99 (1H, s, CH=), 10.03 (1H, br, NH); ^{13}C-NMR ($CDCl_3$, TMS) δ 14.2 (CH_3), 28.3 (CH_3), 31.5 (CH_3), 39.6 (CH_3), 61.7 (CH_2), 97.6 (CH=), 98.3 (C), 143.8 (C), 146.2 (C), 147.9 (C), 151.4 (C), 157.4 (C), 163.1 (C); MS(EI): m/z 308 (M^+); *Anal*. Calcd for $C_{13}H_{16}N_4O_5$: C, 50.65; H, 5.23; N, 18.17. Found: C, 50.57; H, 5.23; N, 18.32.

2,3,4,5-Tetrahydropyrimido[4,5-*c*]-1,2-diazepine-5,6,8(1*H*,7*H*,9*H*)-trione (5)

To a solution of **4** (3 mmol, 0.92 g) in EtOH-CH_2Cl_2 (1 : 1, 20 mL) was added sodium borohydride (0.11 g, 3 mmol) at rt. After being stirred for 15 min, the mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with CH_2Cl_2-MeOH (30 : 1) as eluent to give **5** (0.30 g, 32 %). mp 142 °C; IR (KBr) ν 3420 (NH), 1710, 1700, 1670 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$ + D_2O, TMS) δ 1.30 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 3.23 (1H, dd, C<u>H</u>H, *J*=14.6, 8.4 Hz), 3.37 (3H, s, NCH_3), 3.40 (1H, dd, CH<u>H</u>, *J*=14.6, 3.8 Hz), 3.75 (3H, s, NCH_3), 4.10 (3H, s, NCH_3), 4.24 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 4.64 (1H, dd, CH, *J*=8.4, 3.8 Hz); ^{13}C-NMR ($CDCl_3$, TMS) δ 14.2 (CH_3), 28.3 (CH_3), 31.4 (CH_3), 32.4 (CH_2), 39.1 (CH_3), 61.5 (CH_2), 69.8 (CH), 99.7 (C), 144.0 (C), 146.7 (C), 151.5 (C), 158.5 (C), 173.6 (C); MS(CI): m/z 311 (M^+ + 1); *Anal*. Calcd for $C_{13}H_{18}N_4O_5$: C, 50.32; H, 5.85; N, 18.06. Found: C, 49.99; H, 5.58; N, 17.88.

6-(1,2-Diethoxycarbonylethylidene)hydrazino-3-methyl-2-methylthiopyrimidin-4(3*H*)-one (8)

A mixture of **7** (10 mmol, 2.00 g) and diethyl oxalacetate sodium salt (15 mmol, 3.15 g) was treated in the same manner as described above for **3** to give **8** (2.67 g, 72 %). mp 105 °C; IR (KBr) ν 1740, 1710, 1650 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.25 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 1.38 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 2.56 (3H, s, SCH_3), 3.47 (3H, s, NCH_3), 3.53 (3H, s, NCH_3), 3.77(2H, s,CH_2), 4.19 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 4.37 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 5.90 (1H, s, CH=); ^{13}C-NMR ($CDCl_3$, TMS) δ 13.9 (CH_3), 14.0 (CH_3), 14.9 (CH_3), 29.7 (CH_3), 35.7 (CH_2), 37.8 (CH_3),

61.4 (CH_2), 62.2 (CH_2), 87.6 (CH=), 145.8 (C), 159.9 (C), 162.3 (C), 162.8 (C), 164.3 (C), 168.1 (C); MS(EI): m/z 370 (M^+); *Anal.* Calcd for $C_{15}H_{22}N_4O_5S$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.30; H, 5.90; N, 14.84.

4,5-Dihydropyrimido[4,5-*c*]-1,2-diazepine-5,6(1*H*,7*H*)-dione (9)

The hydrazone (**8**, 3 mmol, 1.11 g) was treated in the same manner as described for the preparation of **4** to give **9** (0.80 g, 82 %). mp 221 °C (MeOH); IR (KBr) ν 1710, 1700 (C=O) cm^{-1}; UV : 300.5 (4.35) and 233.5 (4.35); ^{1}H-NMR ($CDCl_3$, TMS) δ 1.37 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 2.65 (3H, s, SCH_3), 3.46 (3H, s, NCH_3), 3.67 (2H, s, CH_2), 3.83 (3H, s, NCH_3), 4.37 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz); ^{13}C-NMR ($CDCl_3$, TMS) δ 14.1 (CH_3), 15.0 (CH_3), 30.1 (CH_3), 43.4 (CH_3), 46.6 (CH_2), 62.9 (CH_2), 102.3 (C), 145.7 (C), 155.7 (C), 158.9 (C), 161.7 (C), 164.6 (C), 177.1 (C); MS(EI): m/z 324 (M^+); *Anal.* Calcd for $C_{13}H_{16}N_4O_4S$: C, 48.14; H, 4.97; N, 17.27. Found: C, 48.30; H, 5.02; N, 17.44.

6-Ethoxycarbonyl-1,3,5,7-tetramethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (14) and 6-Ethoxycarbonyl-1,3,5-trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (15)

To a solution of **1** (10 mmol, 1.84 g) in acetic acid (20 mL) was added dropwise **12** (20 mmol, 3.89 mL) and the reaction mixture was stirred for 24 h at rt. After evaporation of the solvent under reduced pressure below 30 °C, the residue was chromatographed on a silica gel column with CH_2Cl_2-MeOH (50 : 1) as eluent to give **14** (0.34 g, 12 %) and **15** (0.76 g, 29 %). The analytical samples were purified by recrystallization from EtOH-n-hexane.

14: mp 190.5-191.5 °C; IR (KBr) ν 1690, 1665 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.39 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 2.64 (3H, s, CH_3), 3.37 (3H, s, NCH_3), 3.74 (3H, s, NCH_3), 3.98 (3H, s, NCH_3), 4.34 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz); ^{13}C-NMR ($CDCl_3$, TMS) δ 10.8 (CH_3), 13.4 (CH_3), 27.0 (CH_3), 33.3 (CH_3), 34.7 (CH_3), 59.5 (CH_2), 100.0 (C), 119.6 (C), 128.4 (C), 141.9 (C), 151.5 (C), 158.4 (C), 160.9 (C); MS(CI): m/z 280 (M^+ + 1); *Anal.* Calcd for $C_{13}H_{17}N_3O_4$: C, 55.85; H, 6.13; N, 15.05. Found: C, 55.58; H, 6.11; N, 14.76.

15: mp 260 °C; IR (KBr) ν 3275 (NH), 1710, 1660 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, TMS) δ 1.32 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 2.47 (3H, s, CH_3), 3.16 (3H, s, NCH_3), 3.44 (3H, s, NCH_3), 4.28 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 11.82 (1H, br, NH); ^{13}C-NMR (DMSO-d_6, TMS) δ 10.9 (CH_3), 14.3 (CH_3), 27.3 (CH_3), 30.7 (CH_3), 59.8 (CH_2), 99.6 (C), 116.7 (C), 126.4 (C), 140.2 (C), 150.7 (C), 158.9 (C), 160.9 (C); MS(CI): m/z 266 (M^+ + 1); *Anal.* Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84.

Found: C, 54.34; H, 5.78; N, 15.94.

6-Ethoxycarbonyl-2-methylthio-3,5,7-trimethylpyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (24) and 1,6-Dimethyl-7-methylthiolpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione (25)

A mixture of **7** (10 mmol, 2.00 g) and **12** (20 mmol, 3.89 mL) was treated in the same manner as described above for the preparation of **14** and **15** to give **24** (0.12 g, 4 %) and **25** (0.68 g, 20 %).

24: mp 181-182 °C (EtOH-n-hexane); IR (KBr) ν 1705, 1690 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.41 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 2.63 (3H, s, CH_3), 2.70 (3H, s, CH_3), 3.53 (3H, s, NCH_3), 3.92 (3H, s, NCH_3), 4.36 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz); ^{13}C-NMR ($CDCl_3$, TMS) δ 12.0 (CH_3), 14.4 (CH_3), 15.2 (CH_3), 29.4 (CH_3), 31.0 (CH_3), 60.2 (CH_2), 103.1 (C), 120.3 (C), 126.4 (C), 147.7 (C), 159.3 (C), 159.6 (C), 162.3 (C); MS(EI): m/z 295 (M^+); *Anal.* Calcd for $C_{13}H_{17}N_3O_3S$: C, 52.87; H, 5.80; N, 14.23. Found: C, 53.08; H, 5.81; N, 14.20.

25: mp 187-188 °C (EtOH); IR (KBr) ν 1725, 1695 (C=O) cm^{-1}; UV : 275.0 (4.56); ^{1}H-NMR ($CDCl_3$, TMS) δ 1.15 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 1.39 (3H, d, CH_3, *J*=7.2 Hz), 2.58 (3H, s, SCH_3), 3.44 (3H, s, NCH_3), 3.88 (3H, s, NCH_3), 4.01 (1H, q, CH, *J*=7.2 Hz), 4.08 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz); ^{13}C-NMR ($CDCl_3$, TMS) δ 14.0 (CH_3), 14.1 (CH_3), 15.2 (CH_3), 29.9 (CH_3), 40.6 (CH), 41.1 (CH_3), 60.8 (CH_2), 102.8 (C), 152.9 (C), 157.0 (C), 157.6 (C), 167.0 (C), 168.0 (C), 172.7 (C); MS(EI): m/z 338 (M^+); *Anal.* Calcd for $C_{14}H_{18}N_4O_4S$: C, 49.69; H, 5.36; N, 16.56. Found: C, 49.88; H, 5.37; N, 16.71.

4-Hydrazino-6-methyl-2-pyrone (27)

To a mixture of 4-hydroxy-6-methyl-2-pyrone (0.10 mol, 12.61 g) and anhydrous K_2CO_3 (0.30 mol, 41.46 g) in CH_2Cl_2 (300 mL) at 0 °C was added methylsulfonyl chloride (0.10 mol, 7.74 mL). After being stirred for 2 h at rt, the reaction mixture was washed with water (100 mL) and saturated brine (100 mL), and then the organic layer was dried over anhydrous $MgSO_4$. The drying agent was filtered off and to the filtrate was added anhydrous K_2CO_3 (0.22 mol, 30.41 g) and methylhydrazine (0.22 mol, 11.70 mL). After being stirred for 8 h at room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated brine (100 mL). The crude product obtained upon removal of CH_2Cl_2 was recrystallized from EtOH-isopropyl ether to give **27** (10.02 g, 65 %). mp 164.5-165.5 °C; IR (KBr) ν 3290, 3190 (NH), 1680 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 2.08 (3H, s, CH_3), 3.11 (3H, s, NCH_3), 3.94 (2H, s, NH_2), 4.91 (1H, d, CH=, *J*=2.4 Hz), 6.25 (1H, d, CH=, *J*=2.4 Hz); ^{13}C-NMR

(DMSO-d_6, TMS) δ 19.7 (CH_3), 41.3 (CH_3), 78.3 (CH=), 96.0 (CH=), 159.7 (C), 160.2 (C), 163.5 (C); MS(EI): m/z 154 (M^+); *Anal.* Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.36; H, 6.41; N, 18.32.

4-[1-Methyl-2-(1-phenyl-2-ethoxycarbonylvinyl)hydrazino]-2-pyrone (29)

To a solution of **27** (12 mmol, 1.85 g) in acetic acid (20 mL) was added **28** (24 mmol, 4.16 mL) and the mixture was stirred for 2 days at rt. After evaporation of the solvent under reduced pressure below 30 °C, water (100 mL) was added to the residue and the solvent was extracted with CH_2Cl_2 (100 mL x 3). The organic layer was evaporated and EtOH (10 mL) was added to the residue. The resulting crystals were collected and recrystallized from CH_2Cl_2-n-hexane to give ***29*** (3.00 g, 76 %). mp 139 °C; IR (KBr) ν 1720, 1660 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.32 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 2.23 (3H, s, CH_3), 2.84 (3H, s, NCH_3), 4.21 (2H, q, $OC\underline{H}_2CH_3$, *J*=7.2 Hz), 5.05 (1H, s, CH=), 5.07 (1H, s, CH=), 6.10 (1H, s, CH=), 7.24-7.44 (5H, m, Ph), 9.85 (1H, s, NH); ^{13}C-NMR ($CDCl_3$, TMS) δ 14.3 (CH_3), 20.3 (CH_3), 40.0 (CH_3), 59.8 (CH_2), 82.8 (CH=), 92.7 (CH=), 95.5 (CH=), 127.4 (CH), 128.4 (CH), 130.2 (CH), 133.8 (C), 159.9 (C), 162.0 (C), 162.5 (C), 164.5 (C), 169.5 (C); MS(EI): m/z 328 (M^+); *Anal.* Calcd for $C_{18}H_{20}N_2O_4$: C, 65.80; H, 6.14; N, 8.53. Found: C, 65.72; H, 6.24; N, 8.62

4,5-Dihydropyrano[4,3-*c*]-1,2-diazepine-5,6(1*H*,7*H*)-dione (30)

To PPA (10.0 g) at 90-100 °C was added **29** (3 mmol, 0.99 g) gradually and the reaction mixture was kept at 90-100 °C. After being stirred for an additional 1.5 h at 90-100 °C, the oily reaction mixture was diluted with water (100 mL) while being stirred. The resulting crystals were filtered off and recrystallized from EtOH to give **30** (0.71 g, 84 %). mp 274 °C; IR (KBr) ν 1725, 1655 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 2.24 (3H, s, CH_3), 3.72 (3H, s, NCH_3), 3.75 (2H, s, CH_2), 6.12 (1H, s, CH=), 7.30-7.50 (3H, m, Ph), 7.82-7.95 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$, TMS) δ 20.7 (CH_3), 44.4 (CH_3), 48.5 (CH_2), 96.1 (CH=), 100.3 (C), 127.5 (CH), 125.6 (CH), 131.3 (CH), 133.2 (C), 154.8 (C), 156.4 (C), 158.9 (C), 163.2 (C), 174.8 (C); MS(EI): m/z 282 (M^+); *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C,68.08; H, 5.00; N, 9.86. Found: C, 67.99; H, 4.92; N, 9.86.

5,5-Dimethyl-3-(1-methylhydrazino)-2-cyclohexen-1-one (31)

To a mixture of 5,5-dimethyl-3-mesyloxy-2-cyclohexen-1-one[9] (0.1 mol, 21.83 g) and anhydrous K_2CO_3 (0.22 mol, 30.41 g) in CH_2Cl_2 (300 mL) was added dropwise methylhydrazine (0.22 mol, 11.70 mL). After being stirred for 8 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (100 mL) and

saturated brine (100 mL). After evaporation of CH_2Cl_2 under reduced pressure, the residue was purified by a silica gel column chromatography (CH_2Cl_2 : MeOH = 25 : 1) to give **31** (7.07 g, 42 %). The analytical sample was purified by recrystallization from CH_2Cl_2-petroleum ether. mp 117.5-118.5 °C; IR (KBr) ν 3275, 3175 (NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.02 (6H, s, CH_3 x 2), 2.07 (2H, s, CH_2), 2.42 (2H, s, CH_2), 3.15 (3H, s, NCH_3), 3.88 (2H, s, NH_2), 5.16 (1H, s, CH=); ^{13}C-NMR ($CDCl_3$, TMS) δ 27.8 (CH_3), 31.7 (C), 39.4 (CH_2), 41.6 (CH_3), 48.8 (CH_2), 95.2 (CH=), 165.1 (C), 195.7 (C); MS(EI): m/z 168 (M^+); *Anal.* Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.07; H, 9.72; N, 16.62.

Dehydration of 31 with 28

To a solution of **31** (10 mmol, 1.68 g) in acetic acid (20 mL) was added **28** (20 mmol, 3.46 mL) and the mixture was stirred for 2 days at rt. After evaporation of the solvent under reduced pressure below 30 °C, the residue was purified by a silica gel column chromatography (benzene : ethyl acetate = 1 : 8) to give oily equilibrium mixture of **32** and **32'** (7.07 g, 42 %). IR (KBr) ν 3220 (NH), 1735, 1700, 1660 (C=O) cm^{-1}; MS(EI): m/z 342 (M^+); ^{1}H-NMR ($CDCl_3$, TMS) δ 1.03 (s, CH_3), 1.13 (t, $OCH_2C\underline{H}_3$, *J*=7.4 Hz), 1.24 (t, OCH_2CH_3, *J*=7.4 Hz), 2.07 (s, CH_2), 2.12 (s, CH_2), 2.28 (s, CH_2), 2.82 (s, NCH_3), 3.11 (s, NCH_3), 3.71 (s, $C\underline{H}_2CO_2Et$, *J*=7.4 Hz), 4.06 (q, $OC\underline{H}_2CH_3$, *J*=7.4 Hz), 4.11 (q, $OC\underline{H}_2CH_3$, *J*=7.4 Hz), 4.92 (s, CH=), 5.12 (s, CH=), 7.13-7.50 (m, Ph), 9.74 (s, NH); ^{13}C-NMR ($CDCl_3$, TMS) δ 13.0 ($OCH_2\underline{C}H_3$), 13.4 ($OCH_2\underline{C}H_3$), 27.6 (CH_3), 35.0 ($\underline{C}H_2CO_2Et$), 39.1 (NCH_3), 39.2 (CH_2), 40.0 (NCH_3), 48.7 (CH_2), 48.9 (CH_2), 58.7 ($O\underline{C}H_2CH_3$), 60.6 ($O\underline{C}H_2CH_3$), 90.4 (CH=), 98.6 (CH=), 126.3 (CH), 126.5 (CH), 127.3 (CH), 127.7 (CH), 129.0 (CH), 130.5 (CH), 133.1 (C), 134.3 (C), 161.0 (C), 161.6 (C), 163.6 (C), 166.7 (C), 167.3 (C), 168.6 (C), 195.9 (C), 196.1 (C).

3-Phenyl-1,8,8-trimethyl-4,5,6,7,8,9-hexahydro-1,2-benzodiazepine-5,6(1*H*)-dione (33)

To PPA (10.0 g) at 90-100 °C was added dropwise a solution of oily equilibrium mixture (3.8 mmol, 1.30 g) of **32** and **32'** in toluene (10 mL) and the reaction mixture was kept at 90-100 °C. After being stirred for an additional 0.5 h at 90-100 °C, the toluene layer was decanted from the reaction mixture, and the oily residue was diluted with water (100 mL) while being stirred. The resulting crystals were filtered off and recrystallized from EtOH-$CHCl_3$ to give **33** (0.71 g, 63 %). mp 232 °C; IR (KBr) ν 1675 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, TMS) δ 1.04 (6H, s, CH_3 x 2), 2.09 (2H, s, CH_2), 2.88 (2H, s, CH_2), 3.58 (2H, s,

CH_2), 3.72 (3H, s, NCH_3), 7.40-7.60 (3H, m, Ph), 7.80-7.99 (2H, m, Ph); ^{13}C-NMR (DMSO-d_6, TMS) δ 27.7 (CH_3), 29.8 (C), 42.8 (CH_2), 44.3 (CH_3), 48.1 (CH_2), 50.9 (CH_2), 113.3 (C), 127.6 (CH), 128.8 (CH), 131.3 (CH), 133.1 (C), 155.2 (C), 160.0 (C), 174.1 (C), 191.3 (C); MS(EI): m/z 296 (M^+); *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.70; H, 6.90; N, 9.40.

REFERENCES

1. T. Yamasaki, H. Nakamura, Y. Okamoto, T. Okawara, and M. Furukawa, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1287.
2. T. Yamasaki, E. Kawaminami, T. Yamada, T. Okawara, and M. Furukawa, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 991.
3. W. Sucrow, W. Turnschek, U. Wolf, H. D'Amour, and C. Krüger, *Chem. Ber.*, 1984, **117**, 1620.
4. W. Sucrow, F. Lübbe, and A. Fehlauer, *Chem. Ber.*, 1979, **112**, 1712.
5. F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1484.
6. W. R. Mallory, R. W. Morrison, Jr., and V. L. Styles, *J. Org. Chem.*, 1982, **47**, 667.
7. R. W. Morrison, Jr., W. R. Mallory, and V. L. Styles, *J. Org. Chem.*, 1978, **43**, 4844.
8. F. Yoneda, M. Noguchi, M. Noda, and Y. Nitta, *Chem. Pharm. Bull.*, 1978, **26**, 3154.
9. C.J. Kowalski and K. W. Fields, *J. Org, Chem.*, 1981, **46**, 197.

Received, 22nd April, 1997