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Studies on Heterocyclic Compounds. XII.[1] A Novel Synthesis of 5-Oxo- and 7-Oxo-pyrido[2,3-*d*]pyrimidines

HARUO OGURA and MASAKAZU SAKAGUCHI

School of Pharmaceutical Sciences, Kitasato University[2]

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A simple synthesis of pyrido[2,3-*d*]pyrimidine derivatives as an antitumor agent was reported. Reaction of 6-amino- and 6-(substituted)amino-1,3-dimethyluracil (I) with dimethyl acetylenedicarboxylate in methanol afforded a mixture of 5-oxo- and 7-oxopyrido-[2,3-*d*]pyrimidines and an open-chain intermediate. This intermediate was proved to be 5-substituted 6-aminopyrimidine (VIa), and to be cyclized to 7-oxopyrido[2,3-*d*]pyrimidine (VIIIa). On the other hand, 5-oxo compounds were obtained from the reaction of I with diketene or ethyl acetoacetate.

In previous report,[3] we reported the formation of pyrrolopyrimidines and thienopyrimidines from the reaction of 6-amino-1,3-dimethyluracil or 6-mercapto-1,3-dimethyluracil with α-bromocarbonyl compound. Recently, Shim, *et al.*[4] reported that the reaction of various alkyl-6-aminouracils (I) with dimethyl acetylenedicarboxylate in dimethylformamide (DMF) gave 6-amino-5-(3-methoxycarbonyl-2-propioloyl)uracils (II), and not pyrido[2,3-*d*]pyrimidine derivatives (VIII, IX). It was already reported[5] that the reaction of 5-amino-3-oxo-3,4-dihydropyrazole (III) with dimethyl acetylenedicarboxylate gave 2,7-dioxo-5-methoxycarbonylpyrazolo[1,5-*d*]pyrimidine (IV) and 2,5-dioxo-7-methoxycarbonylpyrazolo[1,5-*a*]pyrimidine (V) in 4: 1 ratio without separation.

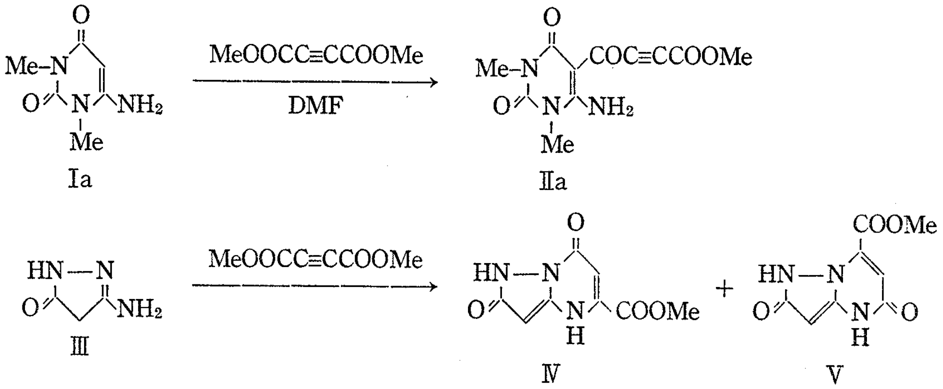

Chart 1

We had reported[6] that the reaction of dimethyl acetylenedicarboxylate with 2-aminobenzothiazole, -benzoxazole, or -benzimidazole gave the cyclized compounds, 2-oxo-4-methoxycarbonylpyrimido[1,2-*a*]-benzothiazole, –benzoxazole, or -benzimidazole. The present

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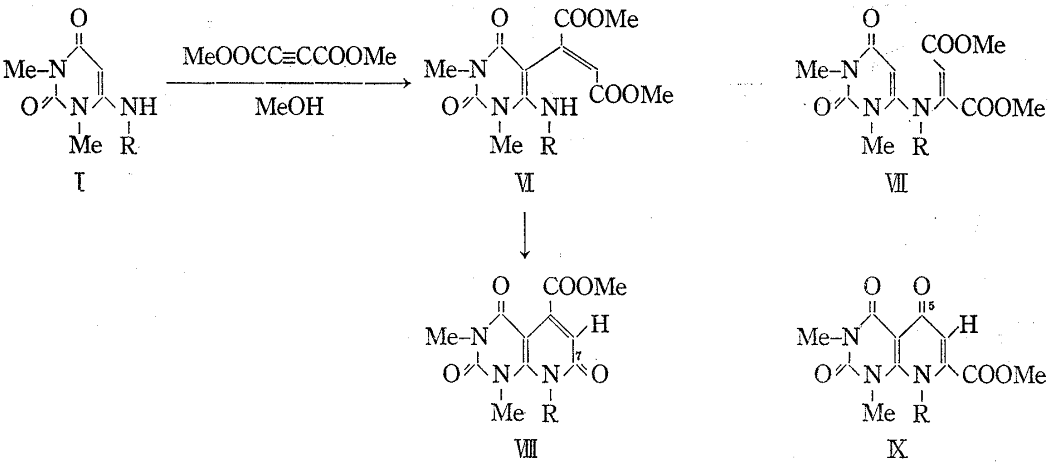
1) Part XI: H. Ogura and K. Kikuchi, *J. Org. Chem.*, 37, 2679 (1972). Preliminaly communication of this paper appeared in *Chem. Letters*, 1972, 657.
2) Location: *Shirokane, Minato-ku, Tokyo, 108, Japan.*
3) H. Ogura, M. Sakaguchi, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 404 (1972).
4) J.L. Shim, R. Niess, and A.D. Broom, *J. Org. Chem.*, 37, 578 (1972).
5) H. Reimlinger, M.A. Peiren, and R. Merenyi, *Chem. Ber.*, **103**, 3252 (1970).
6) H. Ogura, M. Kawano, K. Kikuchi, and T. Itoh, *Abstr. Papers, 3rd Int. Congr. Heterocycl. Chem.*, 1971, 506.

paper describes the reaction of 6-amino-1,3-dimethyluracil (Ia) and substituted amino derivatives (Ib, c, d) with dimethyl acetylenedicarboxylate, diketene, or ethyl acetoacetate. Reaction of 6-(substituted)-amino-1,3-dimethyluracil and its derivatives (Ia, b, c, d) with dimethyl acetylenedicarboxylate in methanol (protic solvent) in place of DMF[4] (aprotic solvent) should produce four kinds of compounds; open-chain compounds (VI and VII), 5-oxo compound (VIII), and 7-oxo compound (IX) (Chart 2). Treatment of Ia with dimethyl acetylenedicarboxylate in methanol at room temperature gave an open-chain compound (VIa), which showed strong bands at 3370 and 3225 cm^{-1} due to an amino group in its infrared (IR) spectrum and did not show C-6 proton as cyclized compound (VIIIa) in its nuclear magnetic resonance (NMR) spectrum. Cyclization to VIIIa occurred on heating of VIa in DMF. From this result, compound (VIIIa) should have 7-oxo group in the molecule. Heating of Ia with dimethyl acetylenedicarboxylate under reflux in methanol produced directly cyclized 7-oxo compound (VIIIa) and a small amount of 5-oxo compound (IXa). From the same reason cited above, the latter (IXa) should have 5-oxo group in the molecule. 5-Oxo compounds (IXa, b, c) show a typical peak for 6-H in their NMR spectrum, δ 7.13, 7.08, 7.42, and 6.85 ppm, respectively. These peaks of 7-oxo compounds (VIIIa, b, c, d) appear in lower magnetic field than those of 5-oxo compounds, δ 6.42, 6.65, 6.34, and 6.36 ppm, respectively. This tendency is similar to those of 2-oxo-4-phenylpyrimido[2,1-*b*]benzimidazole (δ 5.81) and 4-oxo-2-phenylpyrimido[2,1-*b*]benzimidazole (δ 6.30), 2-oxopyrimido[2,1-*b*]benzimidazole (δ 6.05) and 2-methyl-4-oxopyrimido[2,1-*b*]benzimidazole (δ 6.45).[6]



a: R=H b: R=Me c: R=C_6H_5 d: R=$CH_2C_6H_5$

Chart 2

The reaction of 1,3-dimethyl-6-methylaminouracil (Ib) and dimethyl acetylenedicarboxylate gave a mixture of open-chain compounds (VIb, VIIb), and 7-oxo and 5-oxo compounds (VIIIb, IXb). On the other hand, in the case of 6-anilino-1,3-dimethyluracil[7] (Ic), cyclized compounds (VIIIc and IXc) and not an open-chain compound were formed. In the case of 6-benzylamino-1,3-dimethyluracil (Id), a mixture of cyclized compounds (VIIId and IXd) was obtained and this could not be separated by thin-layer chromatography (TLC).

In contrast, Ia, b, c, d reacted with diketene and gave single compounds, 5-oxopyrido-[2,3-*d*]pyrimidines (Xa, b, c, d), and not 7-oxo compound. The position of an oxo group was confirmed by the reaction of Ia with ethyl acetoacetate to yield 6-amino-1,3-dimethyl-2,4-dihydro-5-acetoacetylpyrimidine (*c*; R=H), which showed an amino group from IR spectrum (3450 and 3350 cm^{-1}). This intermediate easily formed 5-oxopyrido[2,3-*d*]pyrimidine (Xa) which was obtained from Ia and diketene. NMR spectrum of Xa shows a peak at δ 6.46

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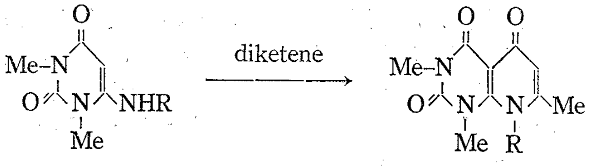
[7] E.C. Taylor and E.E. Garcia, *J. Org. Chem.*, 30, 655 (1965).

ppm (6-H) and the peaks of 8-substituted compound (Xb, c, d) are appeared at δ 6.97, 6.29, and 6.50 ppm, respectively. This result was similar to the reaction of 2-amino-1-methylbenzimidazole with ethyl acetoacetate to yield 2,10-dimethyl-4-oxopyrimido[1,2-*a*]-benzimidazole.[8]



a: R=H b: R=Me c: $R=C_6H_5$ d: $R=CH_2C_6H_5$

Chart 3

These reaction mechanisms of I and dimethyl acetylenedicarboxylate may be represented by the sequence shown in Chart 4. An intermolecular proton transfer from amino group may take two routes, which produces the intermediates *a* and *b* with an olefinic group attached to the C-1 position (*a*) or to the amino group (*b*). These intermediates underwent cyclization to 7-oxo (VIII) or 5-oxo compound (IX). In the case of the reaction of 2-amino-benzothiazole, -benzoxazole, and -benzimidazole with dimethyl acetylenedicarboxylate, there were obtained a single compound, 2-oxopyrimido[2,1-*b*]-benzothiazole, -benzoxazole, and -benzimidazole, in which the proposed reaction mechanisms should take the a type intermediate.[6] On the other hand, the reaction of I and diketene proceeded through the first way via an intermediate (*c*).

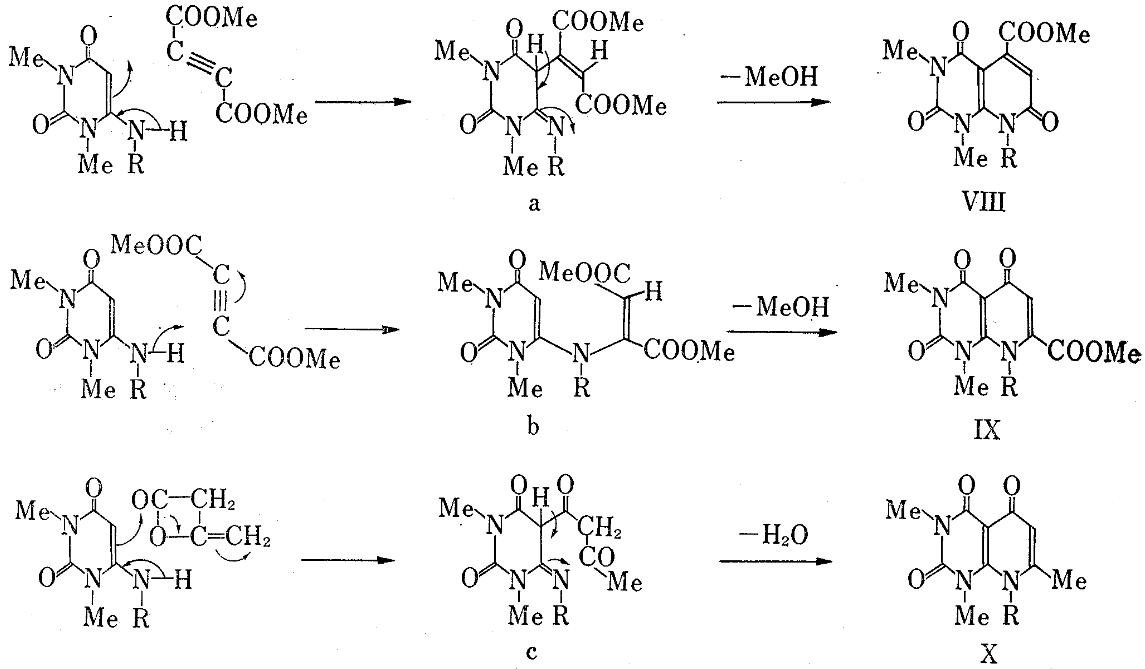


Chart 4

Experimental

Temperatures are uncorrected. NMR spectra were measured in $CDCl_3$ with a Varian T-60 spectrometer with Me_4Si as an internal standard. Mass spectra were measured with JEOL-O1S spectrometer by a direct inlet system at 75 eV.

6-Benzylamino-1,3-dimethyluracil (Id)——A mixture of 6-amino-1,3-dimethyluracil (Ia) (1.55 g, 0.01 mole), benzylamine-HCl (2.16 g, 0.015 mole), and benzylamine (2.0 ml) was heated at 160° for 3 hr. Water was added to the cooled syrupy reaction mixture and the separated solid was collected and recrystallized from DMF to 2.02 g (82%) of Id as white needles, mp 133°, Mass Spectrum *m/e*: 245 (M^+).

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8) Y. Shiokawa and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **19**, 401 (1971).

Reaction of 6-Amino-1,3-dimethyluracil (Ia) with Dimethyl Acetylenedicarboxylate——a) Dimethyl acetylenedicarboxylate (0.71 ml) was added to the solution of Ia (0.62 g, 0.004 mole) in MeOH (25 ml) and the resulting solution was allowed to stand at room temperature for 10 hr. The starting material (Ia) was recovered by filtration and the filtrate was evaporated under a reduced pressure to give a crystalline solid. Recrystallization from EtOH gave 6-amino-1,3-dimethyl-2,4-dihydro-5-(dimethoxycarbonylvinyl)pyrimidine (VIa) (0.28 g, 24%) as yellow plates, mp 186°. *Anal.* Calcd. for $C_{12}H_{15}O_6N_3$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.42; H, 5.05; N, 13.76. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3370, 3225 (NH_2), 1730, 1715, 1692, 1638 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 269 (4.01), 314 (3.67). Mass Spectrum *m/e*: 297 (M$^+$).

b) Dimethyl acetylenedicarboxylate (4.3 ml, 0.03 mole) was added to a solution of Ia (3.1 g, 0.02 mole) in MeOH (100 ml), and the resulting solution was heated under reflux for 6 hr. After evaporation of MeOH, the residual solid was dissolved in $CHCl_3$ and submitted to chromatography on Kieselgel G. Elution with CCl_4–$CHCl_3$ (95: 5) afforded 3.1 g (71%) of 1,3-dimethyl-1,2,3,4,7,8-hexahydro-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-5-carboxylic acid methyl ester (VIIIa) as yellow needles (EtOH), mp 243°. *Anal.* Calcd. for $C_{11}H_{11}O_5N_3$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.93; H, 4.20; N, 15.87. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3280 (NH), 1740, 1710, 1700, 1655, 1645 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 234 (3.99), 264 (3.63), 314 (3.96). NMR δ (ppm): 3.85 (1H, broad, NH), 6.42 (1H, singlet, 6-H). Mass Spectrum *m/e*: 265 (M$^+$).

Subsequent elution of the column with $CHCl_3$ gave 0.05 g (1%) of 1,3-dimethyl-1,2,3,4,5,8-hexahydro-2,4,5-trioxopyrido[2,3-*d*]pyrimidine-7-carboxylic acid methyl ester (IXa) as brownish yellow needles (EtOH), mp 195°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3500 (NH), 1710, 1700, 1670, (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 268 (4.40). NMR δ (ppm): 7.13 (1H, singlet, 6-H). Mass Spectrum *m/e*: 265 (M$^+$).

1,3-Dimethyl-1,2,3,4,7,8-hexahydro-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-5-carboxylic Acid Methyl Ester (VIIIa)——A solution of VIa (0.6 g, 0.002 mole) in DMF (15 ml) was heated at 150° for 5 min. After evaporation of DMF, the residual solid was recrystallized from EtOH to 0.5 g (92%) of VIIIa as yellow needles, mp and mixed mp 243°.

Reaction of 6-Methylamino-1,3-dimethyluracil (Ib) with Dimethyl Acetylenedicarboxylate——Dimethyl acetylenedicarboxylate (2.84 g, 0.02 mole) was added to the solution of Ib (2.50 g, 0.015 mole) in MeOH (50 ml) and the resulting solution was allowed to stand at room temperature for 48 hr. The reaction mixture was concentrated to 20 ml under a reduced pressure and the precipitate was collected by centrifugation to 0.11 g (3%) of white solid (VIb+VIIb) which was washed with a little cold EtOH. This showed one spot on TLC. *Anal.* Calcd. for $C_{13}H_{17}O_6N_3$: C, 50.16; H, 5.50; N, 13.50. Found: C, 49.86; H, 5.47; N, 13.25. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1745, 1713, 1658, 1615 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 275 (4.18), 342 (3.38). Mass Spectrum *m/e*: 297 (M$^+$).

After evaporation of the filtrate, the residual solid was chromatographed on Kieselgel G. Elution with CCl_4–$CHCl_3$ (95: 5) gave 0.6 g (14%) of VIIIb as yellow needles (EtOH). mp 215° (decomp.). *Anal.* Calcd. for $C_{12}H_{13}O_5N_3$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.35; H, 4.60; N, 14.75. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1740, 1700, 1668 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 259 (4.04), 281 (3.81, sh). NMR δ (ppm): 6.65 (1H, singlet, 6-H). Mass Spectrum *m/e*: 279 (M$^+$).

Subsequent elution with the same solvent gave 0.52 g (13%) of IXb as yellow needles (EtOH). mp 230° (decomp.). *Anal.* Calcd. for $C_{12}H_{13}O_5N_3$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.45; H, 4.70; N, 14.83.

Reaction of 6-Anilino-1,3-dimethyluracil (Ic) with Dimethyl Acetylenedicarboxylate——To a solution of Ic (0.6 g) in MeOH (30 ml), dimethyl acetylenedicarboxylate (1.5 ml) was added. After standing the solution at room temperature for 48 hr, the solvent was removed under a reduced pressure. Resulted residue was submitted to chromatography on Kieselgel G, and eluted from CCl_4–$CHCl_3$ (95: 5) gave 0.2 g (23%) of VIIIc as yellow needles (EtOH). mp 217°. *Anal.* Calcd. for $C_{17}H_{15}O_5N_3$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.62; H, 4.45; N, 11.99. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1743, 1710, 1680, 1662 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 286 (3.94), 336 (3.71). NMR δ (ppm): 6.34 (1H, singlet, 6-H). Mass Spectrum *m/e*: 341 (M$^+$).

Subsequent elution with CCl_4–$CHCl_3$ (95: 5—90: 10) gave 0.2 g (23%) of IXc as orange needles (EtOH). mp 187°. *Anal.* Calcd. for $C_{17}H_{15}O_5N_3$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.77; H, 4.30; N, 12.54. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1730, 1665, 1625 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 235 (4.10), 281 (4.30). NMR δ (ppm): 7.42 (6-H). Mass Spectrum *m/e*: 341 (M$^+$).

Reaction of 6-Benzylamino-1,3-dimethyluracil (Id) with Dimethyl Acetylenedicarboxylate——To a solution of Id (1.23 g, 0.005 mole) in MeOH (70 ml), dimethyl acetylenedicarboxylate (1.42 g, 0.01 mole) was added, and the solution was heated under reflux for 3 hr. After evaporation of MeOH, the residual solid was submitted to chromatography on Kieselgel G. Elution with CCl_4–$CHCl_3$ (9: 1) gave 0.5 g (28%) of VIIId +IXd as yellow needles (EtOH). mp 161°. This showed one spot on TLC ($CHCl_3$–MeOH, benzene–acetone, ethylacetate, and/or methylene chloride). *Anal.* Calcd for $C_{18}H_{17}O_5N_3$: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.69; H, 5.04; N, 11.71. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1735, 1705, 1680, 1670 (CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 270 (3.96). NMR δ (ppm): 6.36 (6-H for VIIId), 6.85 (6-H for IXd). Mass Spectrum *m/e*: 355 (M$^+$).

General Procedure for 8-Substituted 1,3,7-Trimethylpyrido[2,3-*d*]pyrimidine-2,4,5(1*H*,3*H*,8*H*)-trione (X)——(a) With Diketene: A mixture of Ia (1.4 g, 0.009 mole) and diketene (10 ml) was stirred at 60—80° for 6 hr. The dark red solution was cooled and the separated pale yellow crystals were collected and recrystallized from benzene to 0.7 g (55%) of Xa as colorless prisms, mp 193°.

Table I. 8-Substituted 5-Oxopyrido[2,3-*d*]pyrimidines (Xa, b, c, d)

Compound	R	mp °C	Yield (%)	IR $\nu_{C=O}^{KBr}$ cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	Formula Mass *m/e* (M+)
Xa	H	193 (colorless prisms)	55	1690 1660	222(4.55) 264(3.64) 300(3.72)	$C_{10}H_{11}O_3N_3.1/2H_2O$ 221
Xb	CH_3	280 (yellow needles)	13	1710 1680	245(4.50) 264(4.02)	$C_{11}H_{13}O_3N_3$ 235
Xc	C_6H_5	280 (280)	40	1715 1675	218(4.18) 247(4.56) 265(4.13)	$C_{16}H_{15}O_3N_3$ 297
Xd	$CH_2C_6H_5$	169 (169)	16	1700 1655	232(4.30) 248(3.93) 264(3.70) 297(3.57)	$C_{17}H_{17}O_3N_3.1/2H_2O$ 311

	Analysis (%)						NMR δ ppm ($CDCl_3$)
	Calcd.			Found			
	C	H	N	C	H	N	
Xa	52.17	5.25	18.25	52.08	4.96	18.55	12.05(1H, s, NH), 6.46(1H, s, CH), 3.62(3H, s, CH_3), 3.41(3H, s, CH_3), 2.46(3H, s, CH_3)
Xd	54.87	5.97	16.25	55.16	5.67	16.56	6.97(1H, s, CH), 4.07(3H, s, CH_3), 3.80(3H, s, CH_3), 3.51(3H, s, CH_3), 2.79(3H, s, CH_3)
Xc	64.64	5.09	14.13	64.37	5.15	14.13	7.41(5H, m, C_6H_5), 6.29(1H, s, CH), 3.35(3H, s, CH_3), 2.88(3H, s, CH_3), 2.03(3H, s, CH_3)
Xd	63.74	5.66	13.12	63.99	5.82	12.95	7.31(5H, m, C_6H_5), 6.50(1H, s, CH), 5.20(2H, s, CH_2), 3.66(3H, s, CH_3), 3.43(3H, s, CH_3), 2.48(3H, s, CH_3)

(b) With Ethyl Acetoacetate: A mixture of Ia (3.1 g. 0.02 mole), ethyl acetoacetate (15 ml), and Et_3N (1 ml) was heated under reflux for 10 hr. The cooled reaction mixture was added to $CHCl_3$ (50 ml) and the starting material (Ia) was filtered off. After evaporation of the filtrate, the residual solid was dissolved in $CHCl_3$ and chromatographed on Kieselgel G. Elution with CCl_4–$CHCl_3$ gave 0.1 g (2%) of Xa as colorless prisms, mp and mixed mp 192°.

Subsequent elution with CCl_4–$CHCl_3$ (9: 1—4: 1) gave 0.05 g (1%) of intermediate (*c*) as colorless needles, mp 244°. *Anal.* Calcd. for $C_{10}H_{13}O_4N_3$: C, 50.21; H, 5.48; N, 17.57. Found: C, 50.46; H, 5.17; N, 17.81. IR ν_{max}^{KBr} cm^{-1}: 3660 (OH), 3450, 3350 (NH_2). UV λ_{max}^{EtOH} nm (log ε): 219 (4.47), 262 (3.70), 304 (4.04). NMR (DMSO-d_6) δ (ppm): 6.31 (1H, singlet, CH), 4.25 (3H, broad, NH_2 and OH), 3.46 (3H, singlet, NMe), 3.23 (3H, singlet, NMe), 2.60 (3H, singlet, Me).

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