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Ring Transformations of 6H-Cyclopropa[5*a*, 6*a*]pyrazolo[1,5-*a*]pyrimidine. II.[1] Reaction of 5a-Acetyl-6a-carbethoxy-5a,6a-dihydro-6H-cyclopropa-[5*a*, 6*a*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles with N-Methylaniline[2]

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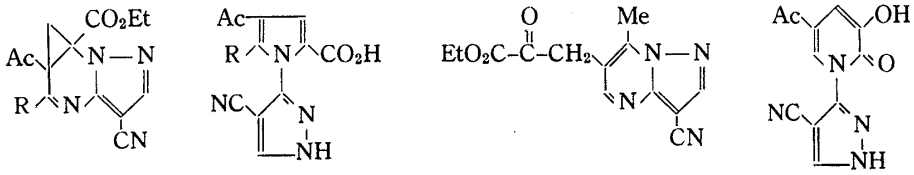
The reaction of 5a-acetyl-6a-carbethoxy-5a,6a-dihydro-6H-cyclopropa[5*a*,6*a*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**1**) with N-methylaniline in refluxing benzene for 20 min afforded four ring-transformed products, namely ethyl E- and Z-*β*-N-methylanilino-6-pyrazolo[1,5-*a*]pyrimidineacrylates (**8** and **9**), N-pyrazolylpyrrole (**10**) and N-pyrazolylpyridone (**11**), together with 4,7-dihydro-7-(N-methylanilino)methylpyrazolo-[1,5-*a*]pyrimidine (**7**). However, the reaction of **2** possessing a methyl group at the 5-position of **1** with N-methylaniline in refluxing xylene gave the 5-methyl derivative of **7** (**13**) and 5-methylpyrazolo[1,5-*a*]pyrimidine (**14**), together with N,N-dimethylaniline. The mechanism of formation of compounds **8**, **9**, **10**, and **11** is discussed.

Keywords——6H-cyclopropa[5*a*,6*a*]pyrazolo[1,5-*a*]pyrimidine; N-methylaniline; N,N-dimethylaniline; ring transformation; N-pyrazolylpyrrole; N-pyrazolylpyridone; NOE; geometrical isomer; keto-enol tautomer

In a recent communication,[1] we reported the ring transformations of 5a-acetyl-6a-carbethoxy-5a,6a-dihydro-6H-cyclopropa[5*a*, 6*a*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles (**1** and **2**) into pyrazolylpyrroles (**3** and **4**), pyrazolylpyridone (**5**), and pyrazolo [1,5-*a*]pyrimidine (**6**) under acidic (AcOH), basic (KOH), and neutral (H_2O) conditions. The formation of these products (**3**—**6**) can be explained by the nucleophilic attack of hydroxy or acetoxy anions at C(6a) of **1** and **2**.



1: R=H
2: R=Me

3: R=H
4: R=Me

6

5

Chart 1

These compounds (**1** and **2**) were also found to react with other nucleophiles such as aliphatic and aromatic amines.[2] Of particular interest among them were the reactions of **1** and **2** with aromatic secondary amines. To extend the scope of these ring transformations, we examined the reactions of **1** and **2** with N-methylaniline.

Reaction of **1** with N-methylaniline in dry benzene at 70—80° for 20 min afforded five products, namely **7** (43.6%) $C_{20}H_{21}N_5O_3$, mp 199—201°, **8** (32.6%) $C_{20}H_{19}N_5O_2$, mp 141—142°, **9** (trace) $C_{20}H_{19}N_5O_2$, mp 157—158°, **10** (4.1%) $C_{13}H_{13}N_4O_3$, mp 213—214°, and **11** (2.3%) $C_{18}H_{15}N_5O_2 \cdot 1/3\ H_2O$, mp 248—251°. The proton magnetic resonance (PMR) spectrum of **7** exhibited, besides two singlet signals at δ 7.60 and 8.00 due to C(5)- and C(2)-protons, an AB quartet signal with a coupling constant (J) of 15 Hz due to the $NC\underline{H}_2$ moiety at δ 3.98 and 4.25. The structure of **7** was confirmed by comparison of its ultraviolet (UV) spectrum [λ_{max}^{EtOH} nm (log ε): 252 (4.25), 312 (4.11), and 385 (3.70)] with that of 6-acetyl-7-carbethoxy-4,7-

dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile.[3] The products **8** and **9** have the same molecular formula, and their infrared (IR), UV and PMR spectral data, and their *Rf* values are summarized in Table I. From these data, they appear to be geometrical isomers with respect to the double bond. It was found that the minor product **9** is the more stable isomer, because the major product **8** isomerized readily to **9** photochemically or by refluxing it in

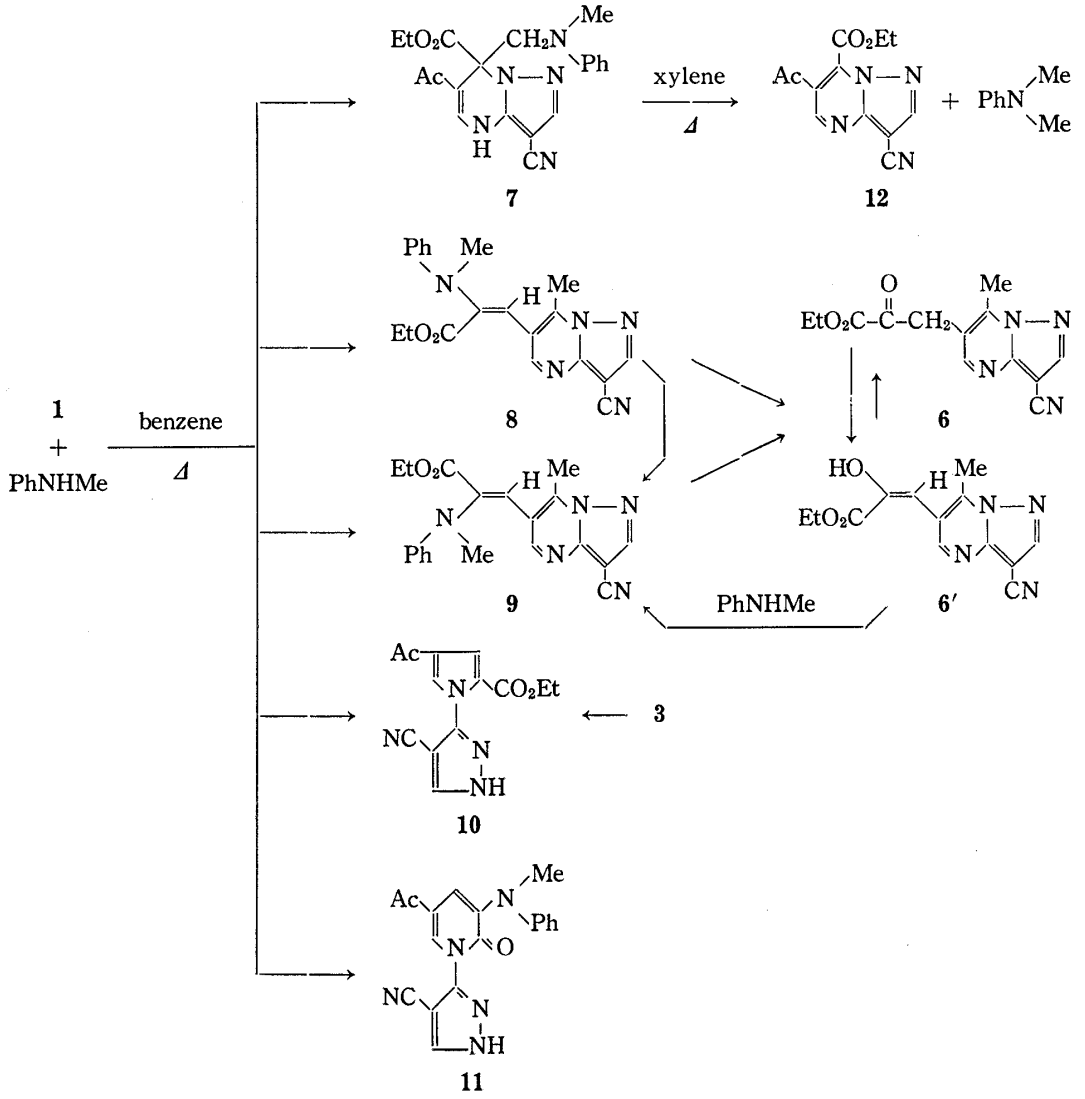


Chart 2

TABLE I. Spectral Data and *Rf* Values for **8** and **9**

Compd. No.	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	PMR (DMSO-d_6) δ	*Rf* value[a]
8	2240, 1730 1605, 1595	230(4.23) 320(4.35)	3.38 (3H, s, NCH_3) 6.33 (1H, s, =CH) NOE 22% NCH_3 ⟶ =CH	0.5
9	2240, 1720 1605	258(4.49) 295(4.20) 373(3.83)	3.02 (3H, s, NCH_3) 7.43 (1H, s, =CH) NOE 0% NCH_3 ⟶ =CH	0.6

a) $Al_2O_3/CHCl_3$.

benzene in the presence of *p*-toluenesulfonic acid (TsOH). The stereostructure of **8** and **9** was elucidated by measurements of intramolecular nuclear Overhauser effects (NOE) as shown in Table I. Irradiation of the N-methyl signal of **8** caused a 22% increase in the integrated intensity of the vinyl proton signal, while irradiation of the N-methyl signal of **9** did not affect the vinyl proton signal. These findings indicate that compound **8** is the E-isomer and **9** is the Z-isomer. This result is consistent with the data that in the PMR spectrum the vinyl proton of **9** resonates at a very low field due to the anisotropic effect of the ethoxycarbonyl group located on the same side. When treated with concentrated hydrochloric acid in ethanol they afforded ethyl 3-cyano-7-methyl-6-pyrazolo[1,5-*a*]pyrimidinepyruvate (**6**), which is known to exist as a mixture (3: 7) of keto (**6**) and enol (**6'**) tautomers.[1)]

Treatment of **6** with N-methylaniline in the presence of TsOH gave **9** in good yield. The structure of product **10** was confirmed on the bases of its spectral data, and by direct comparison with an authentic sample prepared by esterification of compound **3**.[1)] The structure of another product **11** was supported by the spectral data; the IR spectrum showed carbonyl absorption bands at 1685 and 1660 cm^{-1}, and the PMR spectrum showed no $-CO_2CH_2CH_3$ group and exhibited a pair of doublets ($J=2$ Hz) at δ 7.58 and 8.45 due to C(4)- and C(6)-protons as well as a singlet at δ 8.75 due to C(5')-proton. The reaction sequence of **1** with N-methylaniline is thought to proceed as follows. The product **7** may be formed by attack of N-methylaniline at C(6) of **1**. The others (**8**, **9**, **10** and **11**) may be formed through the intermediate B derived by attack of N-methylaniline at C(6a) of **1**; namely the intermediate B is transformed into products **10** and **11** by attack of the 3-amino nitrogen atom on the iminium carbon atom

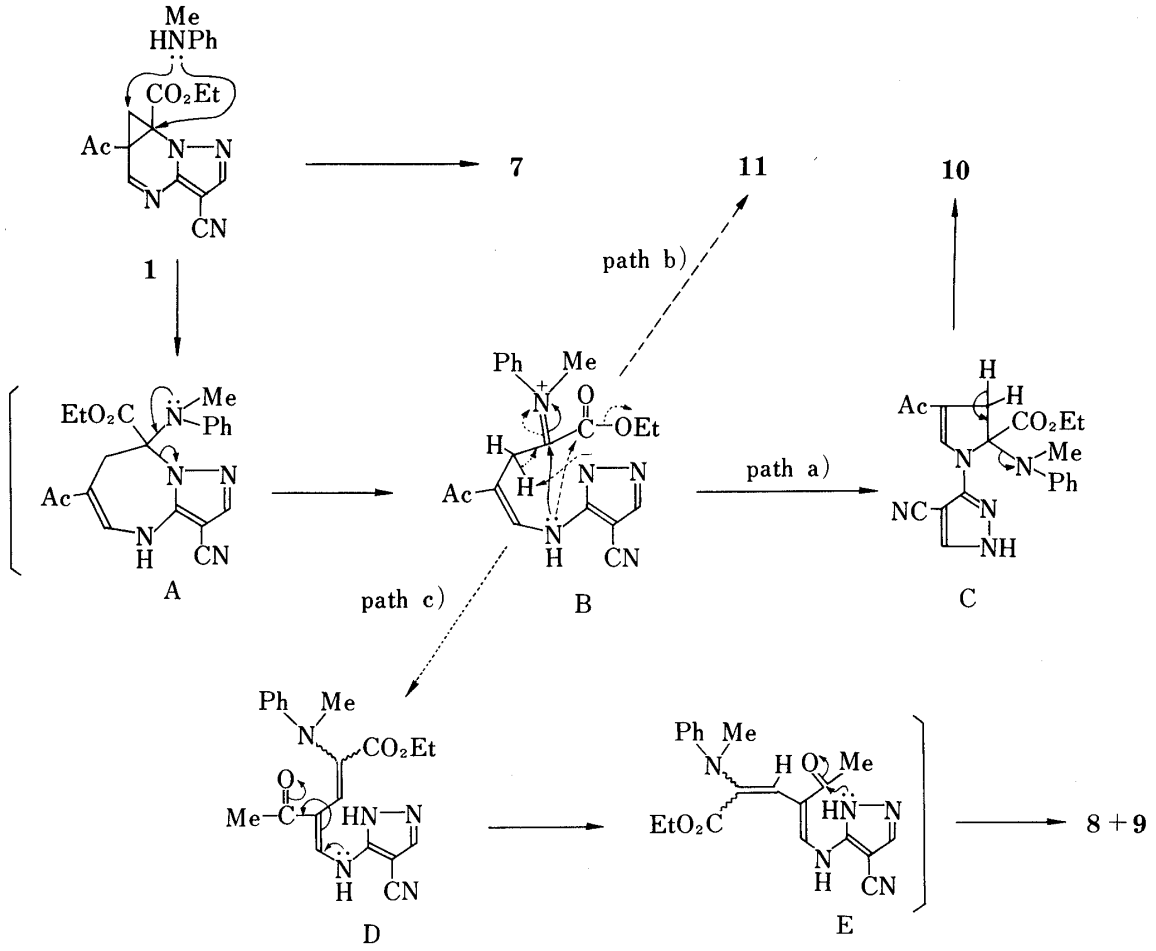


Chart 3

(path a) or the ester carbonyl carbon atom (path b), respectively. On the other hand, when hydrogen abstraction occurred by the ring nitrogen atom (path c), the intermediate E would be formed *via* the intermediate D and this would result in the ultimate formation of the enamines (**8** and **9**) as shown in Chart 3.

Next, the reaction of **2** with N-methylaniline was investigated in refluxing it in xylene, since no reaction takes place in refluxing benzene in this case. After column chromatographic purification of the resulting tarry oil, two crystalline products [**13** (48.6%) $C_{21}H_{23}N_5O_3$, mp 183—184° and **14** (6.3%) $C_{13}H_{12}N_4O_3$, mp 127—128°] were isolated. The structure of **13** was readily determined by comparison of its spectral data with those of **7**. The structure of **14** was also assigned by comparison of its spectral data with those of 6-acetyl-7-carbethoxypyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (12),[3] and furthermore by leading it to **2** upon treatment with diazomethane at room temperature. This compound may be formed through the adduct **13** by the expulsion of N,N-dimethylaniline. The detection of N,N-dimethylaniline in the reaction mixture by gas chromatography strongly supported this view. Indeed, the chemical transformation of **13** as well as **7** was observed by refluxing it in xylene for 3 days to afford **14** and **12**, respectively. Based on these results, it may be concluded that (i) compound **1** is much more subject to ring fission of the cyclopropane ring than compound **2** because the electronegativity of the C(5)=N double bond of **1** is stronger than that of **2** having the electron-donating group at C(5), and (ii) compound **1** is reactive at C(6) and C(6a) to N-methylaniline, whereas **2** is reactive only at C(6).

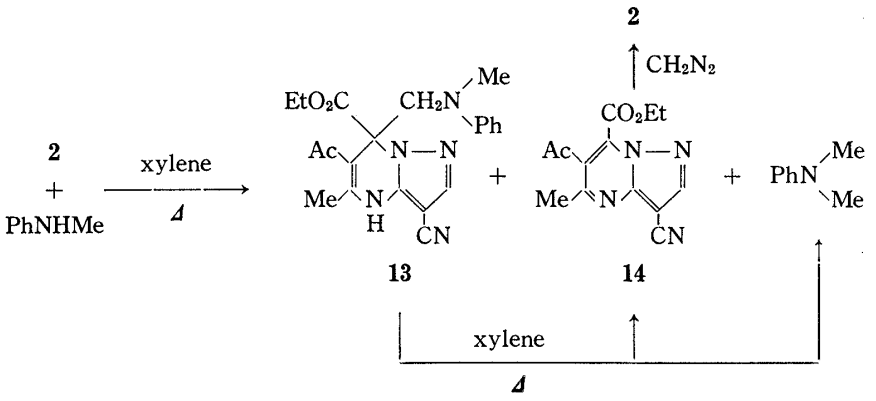


Chart 4

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were recorded with a JASCO model IRA-1 spectrophotometer and the UV spectra with JASCO UVIDEC-505 spectrophotometer. The PMR spectra were recorded with a Hitachi R-24A spectrometer with tetramethylsilane as an internal standard. Gas chromatography was carried out with Shimadzu GC-4BM gas chromatograph equipped with a hydrogen flame ionization detector, and a 3% SE-30 column (column temperature 100°).

Reaction of 1 with N-Methylaniline——A mixture of **1** (3 g) and N-methylaniline (1.128 g) in dry benzene (70 ml) was refluxed for 20 min, then cooled. The resulting precipitate was collected by filtration to give 6-acetyl-7-carbethoxy-4,7-dihydro-7-(N-methylanilino)methylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**7**) (1.644 g, 39.3%) as pale yellow needles of mp 199—201°, after recrystallization from EtOH. IR ν_{max}^{KBr} cm^{-1}: 3200, 2240, 1740 and 1600. UV λ_{max}^{EtOH} nm (log ε): 252 (4.25), 312 (4.11) and 385 (3.70). PMR (DMSO-d_6) δ: 1.10 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.10 (3H, s, $COCH_3$), 2.37 (3H, s, NCH_3), 4.08 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 3.98 and 4.25 (each 1H, each d, J=15 Hz, CH_2), 6.30—7.10 (5H, m, Ar–H), 7.60 (1H, s, C(5)–H), 8.00 (1H, s, C(2)–H) and 11.43 (1H, bs, NH). *Anal.* Calcd for $C_{20}H_{21}N_5O_3$: C, 63.31; H, 5.58; N, 18.46. Found: C, 63.37; H, 5.75; N, 18.65. The filtrate was concentrated *in vacuo* to provide a viscous oil, which crystallized on addition of EtOH. The collected precipitate was recrystallized from EtOH to give ethyl E-β-N-methylanilino-3-cyano-7-methyl-6-pyrazolo[1,5-*a*]pyrimidineacrylate (**8**) (1.30 g, 32.6%) as yellow needles of mp 141—142°. PMR (DMSO-d_6) δ: 0.67 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.72 (3H, s, CH_3), 3.38 (3H, s, NCH_3),

3.82 (2H, q, J=6 Hz, C$\underline{H}_2$CH$_3$), 6.33 (1H, s, CH), 7.0—7.40 (5H, m, Ar–H), 8.55 (1H, s, C(2)–H), and 8.83 (1H, s, C(5)–H). *Anal.* Calcd for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.33; H, 5.25; N, 19.61. The filtrate was concentrated *in vacuo*, and a small volume of $CHCl_3$ was added to the residue. The resulting precipitate was collected by filtration and recrystallized from AcOEt to give ethyl 4-acetyl-1-(4-cyanopyrazol-3-yl)pyrrole-2-carboxylate (**10**) (123 mg, 4.1%) as colorless needles of mp 213—214°. IR ν_{max}^{KBr} cm^{-1}: 3180, 2240, 1710, and 1640. PMR (DMSO-d_6) δ: 1.20 (3H, t, J=6 Hz, CH$_2$C$\underline{H}_3$), 2.43 (3H, s, CH$_3$), 4.15 (2H, q, J=6 Hz, C$\underline{H}_2$CH$_3$), 7.38 (1H, d, J=1.5 Hz, C(3)–H), 8.07 (1H, d, J=1.5 Hz, C(5)–H), and 8.72 (1H, s, C(5′)–H). *Anal.* Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.26; H, 4.45; H, 20.42. The residual oil, which was obtained by evaporation of $CHCl_3$, was subjected to silica gel column chromatography. The first $CHCl_3$ elution gave ethyl Z-β-N-methylanilino-3-cyano-7-methyl-6-pyrazolo-[1,5-*a*]pyrimidineacrylate (**9**) (12 mg, 0.3%) as dark yellow needles of mp 157—158°, after recrystallization from EtOH. PMR (DMSO-d_6) δ: 1.13 (3H, t, J=6 Hz, CH$_2$C$\underline{H}_3$), 2.87 (3H, s, CH$_3$), 3.02 (3H, s, NCH$_3$), 4.15 (2H, q, J=6 Hz, C$\underline{H}_2$CH$_3$), 6.70—7.40 (5H, m, Ar–H), 7.43 (1H, s, CH), 8.60 (1H, s, C(2)–H), and 8.83 (1H, s, C(5)–H). *Anal.* Calcd for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.76; H, 5.44; N, 19.38. The second elution, with 3.3% MeOH in $CHCl_3$, gave an additional crop of **7** (180 mg) (total yield: 43.6%). The third elution, with 3.3% MeOH in $CHCl_3$, gave 5-acetyl-3-N-methylanilino-1-(4-cyanopyrazol-3-yl)-2-pyridone (**11**) (85 mg, 2.3%) as yellow needles of mp 248—251°, after recrystallization from EtOH. IR ν_{max}^{KBr} cm^{-1}: 3160, 2240, 1685, and 1660. UV λ_{max}^{EtOH} nm (log ε): 247 (4.25) and 335 (3.87). PMR (DMSO-d_6) δ: 2.47 (3H, s, COCH$_3$), 3.25 (3H, s, NCH$_3$), 6.70—7.30 (5H, m, Ar–H), 7.58 (1H, d, J=2 Hz, C(4)–H), 8.45 (1H, d, J=2 Hz, C(6)–H), and 8.75 (1H, s, C(5′)–H). *Anal.* Calcd for $C_{18}H_{15}N_5O_2 \cdot 1/3H_2O$: C, 63.70; H, 4.65; N, 20.46. Found: C, 63.95; H, 4.38; N, 20.64.

Isomerization of 8 to 9——Method a): A catalytic amount of TsOH was added to a solution of **8** (0.5 g) in dry benzene (100 ml), and the mixture was refluxed for 10 hr. The solution was concentrated *in vacuo*, and the residue was recrystallized from EtOH to give **9** (0.42 g), which was identified by mixed melting point determination and IR comparison with an authentic sample.

Method b): A solution of **8** (0.4 g) in dry dioxane (500 ml) was irradiated under a nitrogen atmosphere with a 500 W high pressure mercury lamp (Eikosha PIH-500) for 5 hr. The solution was concentrated *in vacuo*, and the residue was recrystallized from EtOH to give **9** (250 mg), which was identified by mixed melting point determination and IR comparison with an authentic sample.

Treatment of 8 (or 9) with Hydrochloric Acid in Ethanol——A mixture of **8** (or **9**) (0.2 g), and conc. HCl (3 ml) in EtOH (30 ml) was allowed to stand for 1 hr. The solution was concentrated *in vacuo*, and the residue was recrystallized from EtOH to give (**6**) (75—80%) of mp 178—179°; this compound is known to exist as a mixture (3:7) of keto (**6**) and enol (**6′**) tautomers. $FeCl_3$ test: positive (dark green). IR ν_{max}^{KBr} cm^{-1}: 3400, 2240, 1710, and 1610. PMR (DMSO-d_6) δ: Data for keto form (**6**) 1.33 (t, J=6 Hz, CH$_2$C$\underline{H}_3$), 2.70 (s, CH$_3$), 4.30 (q, J=6 Hz, CH$_2$C$\underline{H}_3$), 4.47 (s, CH$_2$), 8.60 and 8.75 (each s, C(2)- and/or C(5)–H). Data for enol form (**6′**) 1.33 (t, J=6 Hz, CH$_2$C$\underline{H}_3$), 2.80 (s, CH$_3$), 4.30 (q, J=6 Hz, C$\underline{H}_2$CH$_3$), 6.45 (s, =CH), 8.75 (s, C(2)–H) and 9.25 (s, C(5)–H). *Anal.* Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.36; H, 4.30; N, 20.57.

Reaction of 6 with N-Methylaniline——A catalytic amount of TsOH was added to a solution of **6** (0.2 g) and N-methylaniline (80 mg) in dry benzene (50 ml), and the mixture was refluxed for 20 hr. The solution was concentrated *in vacuo*, and the residue was recrystallized from EtOH to give **9** (225 mg), which was identified by mixed melting point determination and IR comparison with an authentic sample.

Esterification of 3——A solution of **3** (0.1 g) in a mixture of EtOH (30 ml) and benzene (45 ml) in the presence of one drop of conc. sulfuric acid was refluxed for 2 days in a Soxhlet apparatus in order to remove water as it was formed. The solution was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with $NaHCO_3$ solution, water, and dried. After removal of the solvent by evaporation, the residue was recrystallized from AcOEt to give **10** (24 mg), which was identified by IR comparison with an authentic sample.

Reaction of 2 with N-Methylaniline——A mixture of **2** (1.446 g) and N-methylaniline (0.6 g) in dry xylene (80 ml) was refluxed for 20 hr. The solution was concentrated *in vacuo*, and the resulting tarry oil was subjected to silica gel column chromatography. The first $CHCl_3$ elution gave 6-acetyl-7-carbethoxy-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**14**) (88 mg, 6.3%) as colorless needles of mp 127—128°, after recrystallization from EtOH. IR ν_{max}^{KBr} cm^{-1}: 2240, 1750, 1690 and 1615. PMR (DMSO-d_6) δ: 1.33 (3H, t, J=6 Hz, CH$_2$C$\underline{H}_3$), 2.65 and 2.73 (each 3H, each s, CH$_3$ and/or COCH$_3$), 4.47 (2H, q, J=6 Hz, C$\underline{H}_2$-CH$_3$) and 8.90 (1H, s, C(2)–H). *Anal.* Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.35; H, 4.43; N, 20.38. The second $CHCl_3$ eluate gave 6-acetyl-7-carbethoxy-4,7-dihydro-5-methyl-7-(N-methylanilino)methylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**13**) (0.95 g, 48.6%) as pale yellow needles of mp 182—183°, after recrystallization from AcOEt–*n*-Hexane. IR ν_{max}^{KBr} cm^{-1}: 3250, 2240, 1750 and 1640. UV λ_{max}^{EtOH} nm (log ε): 254 (4.21) and 313 (4.12). PMR (DMSO-d_6) δ: 1.13 (3H, t, J=6 Hz, CH$_2$C$\underline{H}_3$), 2.07 (3H, s, COCH$_3$), 2.23 (3H, s, CH$_3$), 2.40 (3H, s, NCH$_3$), 4.07 (2H, q, J=6 Hz, C$\underline{H}_2$CH$_3$), 3.90 and 4.25 (each 1H, each d, J=15 Hz, CH$_2$), 6.40—7.15 (5H, m, Ar–H) 7.95 (1H, s, C(2)–H) and 10.85 (1H, s, NH). *Anal.* Calcd for $C_{21}H_{23}N_5O_3$: C, 64.11; H, 5.89; N, 17.80. Found: C, 63.83; H, 5.91; N, 18.07.

Treatment of 14 with Diazomethane——Compound **14** (100 mg) was added to a solution of diazomethane in ether with stirring at room temperature. After stirring had been continued for 2 hr, the solution was evaporated to dryness. The residue was recrystallized from EtOH to give **2**, which was identified by IR comparison with an authentic sample.

Pyrolysis of 7 (or 13) in Xylene——A solution of **7** (or **13**) (200 mg) in dry xylene (50 ml) was refluxed for 3 days. After removal of the solvent by evaporation, the residue was recrystallized from EtOH to give **12** (53 mg) and **14** (55 mg), which were identified by IR comparison with the corresponding authentic samples.

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References and Notes

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