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Ring Transformations of 6H-Cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine. III.¹⁾
Synthesis and X-Ray Crystal Structure Determination of a
1-Pyrazol-3-ylpyrrole-2-carboxylic Acid

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Ring transformations and ring expansions of 5a-acetyl-5a,6a-dihydro-6a-ethoxycarbonyl-6H-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidines (3, 4 and 5) are described. For example, treatment of **4a** with potassium hydroxide in ethanol gave 4-acetyl-1-(4-cyanopyrazol-3-yl)-5-methylpyrrole-2-carboxylic acid (**7a**), the structure of which was confirmed by X-ray crystal structure determination. On the other hand, it was found that **3a** reacted with ethanol, with ethanol in the presence of potassium hydroxide, or with acetic acid to give 7,8-dihydro-8-ethoxy(or acetoxy)-4H-pyrazolo[1,5-*a*][1,3]diazepines (**17**, **11** or **24**, respectively) in moderate yields. Furthermore, when aqueous dioxane was used as the reaction medium, **3a** was transformed to ethyl 6-pyrazolo[1,5-*a*]pyrimidinepyruvate (**22**), which was found to exist as a mixture of keto and enol tautomers. The mechanism of formation of these products is discussed.

Keywords—6H-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine; ring transformation; ring expansion; X-ray analysis, 1-pyrazol-3-ylpyrrole; 4H-pyrazolo[1,5-*a*][1,3]diazepine; 1-pyrazol-3-ylpyridone; keto-enol tautomer

The reaction of diazomethane with heterocyclic compounds has been widely investigated.²⁾ Coumarins bearing an acetyl group at position 3 are known to be methylated by diazomethane at position 4.³⁾ In contrast, 3-acetylcoumarin undergoes sequential ring expansions with diazomethane to oxepin, oxocin and oxonium derivatives.⁴⁾ Dean *et al.*⁵⁾ also reported a steric effect in the ring expansion of coumarins having an electron-withdrawing group at position 3 by 2-diazopropane and *t*-butyldiazomethane. In general, chromones activated by an electron-withdrawing group at position 3 are alkylated at position 2 by diazoalkanes in the same manner as the isomeric coumarins.⁶⁾ Recently, we reported⁷⁾ ring transformations of 5a-acetyl-5a,6a-dihydro-6a-ethoxycarbonyl-6H-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**3a**) and its 5-methyl derivative (**4a**), which were readily obtained by the reaction of 6-acetyl-7-ethoxycarbonylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**1a**) with diazomethane.⁸⁾ The present paper describes further reactions of the cyclopropane derivatives⁸⁾ and gives a full account of work described in a previous communication.⁷⁾

Treatment of **4a** with an equimolar amount of potassium hydroxide (KOH) in 98% ethanol at room temperature gave a carboxylic acid, C₁₂H₁₀N₄O₃, mp 279—280°C, as colorless needles in 69.7% yield. The product exhibited characteristic bands due to NH, CN, COOH and COCH₃ groups (3300, 2240, 1720 and 1660 cm⁻¹, respectively) in the infrared (IR) spectrum. The nuclear magnetic resonance (NMR) spectrum suggested the presence of two aromatic protons in the molecule, showing signals at δ 7.39 and 8.63 ppm (each 1H, each s) together with signals due to a methyl and an acetyl group at δ 2.23 and 2.41 ppm (each 3H, each s), respectively. On the basis of these spectral data, the structure of the product was tentatively presumed to be 6-acetyl-3-cyano-5-methyl-4H-pyrazolo[1,5-*a*][1,3]diazepine-8-carboxylic acid (**6**), formed through the ring expansion of the cyclopropane ring with hydrolysis of the ester group. However, no characteristic absorption maximum was observed in its ultraviolet (UV) spectrum. Treatment of this product with diazomethane in ether gave rise to a dimethylated product (**9a**), mp 197—199°C, whose NMR spectrum showed the presence of COOCH₃ and

NCH₃ groups. Thus, in order to obtain definitive evidence for the structure of the carboxylic acid, an X-ray crystallographic analysis was carried out and the structure was unambiguously established as 4-acetyl-1-(4-cyanopyrazol-3-yl)-5-methylpyrrole-2-carboxylic acid (**7a**), as shown in Fig. 1. Hence, the structure of **9a** was determined to be methyl 4-acetyl-1-(4-cyano-1-methylpyrazol-3-yl)-5-methylpyrrole-2-carboxylate.

Fig. 1. Stereoscopic View of the Molecule of **7a**

TABLE I. Physical Data for 1-Pyrazol-3-ylpyrrole-2-carboxylic Acids

Compd. No.	mp(°C)	Yield (%)	Formula	Analyses (%)		
				Calcd (Found)	C	H N
7a	279—280 (EtOH) ^a	69.7	C ₁₂ H ₁₀ N ₄ O ₃	55.81 (55.91)	3.90 (4.02)	21.70 (21.67)
7b	234—235 (H ₂ O) ^a	80.5	C ₁₂ H ₁₂ N ₄ O ₄	52.17 (52.31)	4.38 (4.45)	20.28 (20.25)
7c	274—277 (EtOH-H ₂ O) ^a	56.1	C ₁₃ H ₁₄ N ₄ O ₄	53.79 (53.68)	4.86 (4.98)	19.30 (19.01)
8b	156—157 (H ₂ O) ^a	42.4	C ₁₃ H ₁₄ N ₄ O ₅	50.98 (50.84)	4.61 (4.61)	18.29 (18.43)

^a) Recrystallization solvent.

Under the same experimental conditions, other derivatives (**4b**, **4c** and **5b**) of **4a** were transformed to 1-pyrazol-3-ylpyrroles (**7b**, **7c** and **8b**) as summarized in Table I, and this represents a useful synthetic method for the unique 1-pyrazol-3-ylpyrrole-2-carboxylic acids.⁹⁾

A possible mechanism for the ring transformation of **4a** to **7a** is shown in Chart 2; *i.e.*, the first stage might involve nucleophilic attack of the hydroxy anion at the 6a-position accompanying the ring expansion after hydrolysis of the ester group. By prototropy, the α -keto acid intermediate will be formed. Then, the dehydrative cyclization of the 3-amino nitrogen atom to the α -keto carbonyl carbon atom may form **7a**.

Chart 2

These results prompted us to apply the synthetic method for **3** to other heterocycles, and our interest was focused on compound **3a** because of its ready availability and its good solubility in organic solvents.

Firstly, treatment of **3a** with an equimolar amount of KOH in 98% ethanol afforded a carboxylic acid (**11**), mp 115–117°C, in 80.7% yield, whose NMR spectrum {DMSO-*d*₆ δ : 0.92 (3H, t, $J=6$ Hz, OCH₂CH₃), 2.28 (3H, s, COCH₃), 2.78 and 3.48 (each 1H, each d, $J=16$ Hz, CH₂), 3.15 and 3.72 (each 1H, each m, OCH₂CH₃), 7.32 [1H, d, $J=6$ Hz, C(5)-H], 7.89 [1H, s, C(2)-H] and 10.50 (1H, d, $J=6$ Hz, exchanged with D₂O, NH)} suggested the presence of an OCH₂CH₃ group and the absence of a cyclopropane ring. The UV spectrum of **11** [$\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 318 (4.37)] is similar to that of the 4,7-dihydro derivative of **1a**.⁸⁾ Thus, **11** was assigned as 6-acetyl-3-cyano-7,8-dihydro-8-ethoxy-4H-pyrazolo [1,5-*a*][1,3]diazepine-8-carboxylic acid. It should be noted that in the NMR spectrum of **11** the methylene protons of the OCH₂CH₃ group attached to the 8-position showed multiplet signals as shown in Fig. 2. It is documented¹⁰⁾ that when the ethoxy group is attached to a chiral center its methylene group becomes diastereotopic and thus its splitting pattern becomes complicated.

Chart 3

Fig. 2. NMR Spectrum of 8-Ethoxy-pyrazolodiazepine (11) in DMSO- d_6

TABLE II. Physical and Spectral Data for 5-Alkoxy-cyclopropapyrazolopyrimidine Derivatives

Compd. No.	mp (°C)	Yield (%)	Formula	Analyses (%)			IR(KBr) ν cm ⁻¹		
				Calcd (Found)			NH	CN	CO
				C	H	N			
13	146—149	32.6	C ₁₄ H ₁₆ N ₄ O ₄	55.25 (55.18)	5.30 (5.58)	18.41 (18.23)	3230	2220	1750 1710
13'	150—153	26.0	C ₁₄ H ₁₆ N ₄ O ₄	55.25 (55.04)	5.30 (5.10)	18.41 (18.39)	3300	2220	1750 1730
14	153—157	40.2	C ₁₅ H ₁₈ N ₄ O ₄	56.59 (56.42)	5.70 (5.87)	17.60 (17.70)	3230	2220	1740 1710
15	145—147	41.4	C ₁₆ H ₂₀ N ₄ O ₄	57.82 (57.98)	6.07 (5.99)	16.86 (16.41)	3240	2220	1740 1710

NMR δ (DMSO- d_6) (J =Hz)									
Compd. No.	R	CO ₂ CH ₂ CH ₃ (J =6)	(J =6)	COCH ₃	CHOR (J =3)	NH (J =3)	C ₂ -H	OR	
13	Me	1.23(3H, t) 4.22(2H, q)	1.78(d) 2.53(d)	2.35	5.14(d)	6.60(bd)	7.60	3.35 (s, OCH ₃)	
13'	Me	1.35(3H, t) 4.40(2H, q)	1.65(d) 2.10(d)	2.38	5.25(d)	7.35(bd)	7.58	3.45 (s, OCH ₃)	
14	Et	1.22(3H, t) 4.20(2H, q)	1.78(d) 2.50(d)	2.33	5.22(d)	6.42(bd)	7.58	1.20 (t, J =6, OCH ₂ CH ₃) 3.55 (m, OCH ₂ CH ₃)	
15	<i>n</i> -Pr	1.21(3H, t) 4.18(2H, q)	1.78(d) 2.48(d)	2.33	5.18(d)	6.46(bd)	7.55	1.86 (t, J =6, OCH ₂ CH ₂ CH ₃) 1.56 (m, OCH ₂ CH ₂ CH ₃) 3.42 (m, OCH ₂ CH ₂ CH ₃)	

Similarly, treatment of **3a** with KOH in 98% methanol or *n*-propanol gave the corresponding 8-methoxy or 8-propoxy derivative (**10**, **12**).

Secondly refluxing of **3a** in methanol for 1 h afforded two configurational isomers of 5a-acetyl-6a-ethoxycarbonyl-5-methoxy-4,5,5a,6a-tetrahydro-6H-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles (**13**, **13'**) with respect to the C(5)-methoxy group [**13**, mp 148—150°C, 32.6% yield and **13'**, mp 150—152°C, 26.0% yield], which were separated by fractional recrystallization from benzene. However, in the case of ethanol or *n*-propanol, the corresponding alcohol adduct (**14** or **15**) was obtained as a single product in 40.2 or 41.4% yield, respectively. Although the structures of these products were determined on the basis of the analytical and spectral data shown in Table II, it is not possible to assign their stereochemical structures at this stage.

In addition, upon reflux in ROH (R=Me, Et and *n*-Pr) for 5 days, **3a** afforded ethyl 8-alkoxy-6-acetyl-3-cyano-7,8-dihydro-4H-pyrazolo[1,5-*a*][1,3]diazepines (**16**, **17** and **18**), whose structures were determined on the basis of analytical data and by comparison of the spectral data with those of the corresponding carboxylic acids (**10**, **11** and **12**), as summarized in Table III.

Compound **17** was acetylated with acetic anhydride to give the monoacetate (**19**), which showed a clear signal in its NMR spectrum at δ 8.07 as a singlet, assignable to the C(5)-proton shifted downfield by the effect of the N-acetyl group. Although hydrolysis of **13** in 98% ethanolic KOH at room temperature afforded **11** in quantitative yield, **16** was hydrolyzed with difficulty on reflux in 98% ethanolic KOH to give **11** in a poor yield. From the results of the above experiments, it can be concluded that the ester group on the cyclopropane ring is much more subject to hydrolysis than that attached to the 1,3-diazepine ring. Subsequently, refluxing of **11** in water for 10 min gave 4-acetyl-1-(4-cyanopyrazol-3-yl)pyrrole-2-carboxylic acid (**20**) as a major product (45.2%) as well as an unexpected product (**21**), mp 223—225°, in 11.3% yield. The identity of **20** was readily established by comparison of the spectral data with those of **7a**. The compound **21** gave results of elemental analysis consistent with a molecular formula of $C_{11}H_8N_4O_3$ and gave a dark green color with $FeCl_3-K_3[Fe(CN)_6]$ in ethanol, indicating the presence of a enolic hydroxy group. The presence of keto-enol tautomers (**21'** and **21**) was observed and the equilibrium ratio could be estimated from the integral intensities of the signals in the NMR spectrum (DMSO- d_6) to be **21'**: **21**=3: 7. The chemical shifts representing the tautomerism are recorded in Chart 3. On the basis of these results, the structure of the product was assigned to be 3-cyano-7-methyl-6-pyrazolo[1,5-*a*]pyrimidinepyruvic acid (**21**). However, **16** was recovered unchanged when an aqueous dimethylformamide (DMF) solution of **16** was refluxed for 10 h.

The ring transformation of **11** to **20** and **21** probably involves the initial formation of the α -keto acid (intermediate A). Then, while the dehydrative cyclization of the 3-amino nitrogen atom to the α -keto carbonyl carbon atom (path a) may form **20**, **21** would be formed through isomerization of A followed by subsequent dehydrative cyclization of the pyrazole ring nitrogen atom to the acetyl carbonyl carbon atom (path b), as shown in Chart 4.

Thirdly, upon refluxing of **3a** in 80% aqueous dioxane for 10 h, ethyl 3-cyano-7-methyl-6-pyrazolo[1,5-*a*]pyrimidinepyruvate (**22**), which is known to exist as a mixture (3 : 7) of keto (**22'**)

Chart 4

and enol (**22**) tautomers,¹⁾ was obtained in 74% yield. Reaction of **22** with acetic anhydride and pyridine under the usual conditions gave the enol acetate (**23**) in good yield. The stereo-structure of **23** (the E-isomer) was assigned from its NMR spectrum, in which the vinyl proton of the enol form (**22**) appeared at δ 6.50 ppm, whereas that of **23** at δ 7.64 ppm was shifted down field by 1.14 ppm due to the anisotropic effect of the acetoxy group located on the same side.

Chart 5

Finally, the reactivity of **3a** in acidic media was examined. On refluxing of **3a** in glacial acetic acid for 10 min, a new substance was isolated in 62.8% yield; it was assigned as ethyl 8-acetoxy-6-acetyl-3-cyano-7,8-dihydro-4H-pyrazolo[1,5-*a*][1,3]diazepine-8-carboxylate (**24**). The NMR spectrum of **24** showed a signal due to the newly formed acetoxy group at δ 2.08 ppm. Additionally, this product showed 1-proton doublets ($J=16$ Hz) for non-equivalent gem protons on the 7-membered ring at δ 3.30 and 3.60 ppm. Confirmation of the structure (**24**) was provided by the following experiment. Hydrolysis of **24** in aqueous acetic acid afforded **22** in good yield, presumably by the pathway (path b) shown in Chart 4. On the other hand, when **24** was treated with an equimolar amount of KOH in 98% ethanol at room temperature, a crystalline substance (**25**), $C_{11}H_8N_4O_3$, mp $>300^\circ\text{C}$, was isolated in 93% yield. The product gave a dark green color with $\text{FeCl}_3\text{-K}_3[\text{Fe}(\text{CN})_6]$ in ethanol. Treatment of **25** with acetic anhydride and pyridine under ordinary conditions gave the diacetate (**26**). The NMR spectrum of **25** showed the absence of a $\text{CO}_2\text{CH}_2\text{CH}_3$ group and three aromatic protons as two sets of doublets at δ 7.18 and 8.13 ppm ($J=2$ Hz) and a singlet at δ 8.75 ppm. Based on these results, the structure 5-acetyl-3-hydroxy-1-(4-cyanopyrazol-3-yl)-2-pyridone (**25**) was assigned to this product. The transformation of **24** to **25** presumably proceeds in the same way as in the case of that of **4a** to **7a**, to form the α -keto ester intermediate. Then, the 3-amino nitrogen atom attacks the ester carbonyl carbon atom resulting in the formation of **25** as shown in Chart 6.

Chart 6

In contrast with compound **3a**, **4a** was recovered unchanged when ethanol or aqueous dioxane solution of **4a** was refluxed for 3 to 4 days. Furthermore, by refluxing of **4a** in acetic acid for 3 to 4 days, ethyl 4-acetyl-1-(4-carbamoylpyrazol-3-yl)-5-methyl-pyrazole-2-carboxylate (**27**) was obtained in low yield. Thus, by analogy with the reaction of **3a** or **4a** with *N*-methylaniline,¹⁾ the electron-donating group at the 5-position presumably results in a decrease of reactivity. The present study provides a method for the synthesis of the following heterocycles, (i) 7,8-dihydro-4H-pyrazolo[1,5-*a*][1,3]diazepines (**10**, **11**, **12**, **16**, **17**, **18** and **24**) from pyrazolo[1,5-*a*]pyrimidines *via* ring expansion of 6H-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine (**3a**) and (ii) 1-pyrazol-3-ylpyrrole-2-carboxylic acids (**7a**, **7b**, **7c**, **8b** and **20**) or 1-pyrazol-3-yl-2-pyridone (**25**) *via* ring transformation of 6H-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidines (**4a**, **4b**, **4c**, **5b** and **3a**).

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were recorded on a JASCO model IRA-1 spectrophotometer and the UV spectra on a JASCO UVIDE-505 spectrophotometer. The NMR spectra were recorded with a Hitachi R-24A spectrometer in deuteriodimethylsulfoxide. Chemical shifts are given in δ (ppm) relative to tetramethylsilane as an internal standard.

General Procedure for the Preparation of 1-Pyrazol-3-ylpyrrole-2-carboxylic Acids (7a, 7b, 7c and 8b)—A solution of KOH (1.2 mmol) in water (2 ml) was added to a solution of **4a** (or **4b**, **4c**, **5b**) (1 mmol) in EtOH (150 ml) under ice cooling, and then the mixture was allowed to stand for 3 h (in the case of **5b** for 15 h). After removal of the solvent by evaporation, the residue was dissolved in water (5 ml). The aqueous solution was acidified by the addition of conc. HCl under ice cooling. The precipitate was collected by filtration, and recrystallized (Table I).

4-Acetyl-1-(4-cyanopyrazol-3-yl)-5-methylpyrrole-2-carboxylic Acid (7a)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300 (NH), 2240 (CN), 1720, 1660 (CO). NMR δ : 2.23 (3H, s, CH₃), 2.41 (3H, s, COCH₃), 7.39 [1H, s, C(3)-H], 8.63 (1H, s, pyrazole ring-H), 12.50 and 13.87 (each 1H, each bs, COOH and/or NH).

4-Acetyl-1-(4-carbamoylpyrazol-3-yl)-5-methylpyrrole-2-carboxylic Acid (7b)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3460—3360 (OH and NH₂), 1710, 1650 (CO). NMR δ : 2.15 (3H, s, CH₃), 2.40 (3H, s, COCH₃), 6.70—7.30 (2H, bs, CONH₂), 7.31 [1H, s, C(3)-H], 8.31 (1H, s, pyrazole ring-H), 13.26 (1H, bs, COOH or NH).

4-Acetyl-1-(4-N-methylcarbamoylpyrazol-3-yl)-5-methylpyrrole-2-carboxylic Acid (7c)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400—3200 (OH and NH), 1690, 1640 (CO). NMR δ : 2.14 (3H, s, CH₃), 2.40 (3H, s, COCH₃), 2.60 (3H, d, *J*=5 Hz, NHCH₃), 7.31 [1H, s, C(3)-H], 7.82 (1H, d, *J*=5 Hz, NHCH₃), 8.26 (1H, s, pyrazole ring-H), 12.13 and 13.20 (each 1H, each bs, COOH and/or NH).

1-(4-Carbamoylpyrazol-3-yl)-4-ethoxycarbonyl-5-methylpyrrole-2-carboxylic Acid (8b)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3600—2800 (OH and NH), 1710—1650 (CO). NMR δ : 1.28 (3H, t, *J*=6 Hz, CO₂CH₂CH₃), 2.15 (3H, s, CH₃), 4.20 (2H, q, *J*=6 Hz, CO₂CH₂CH₃), 6.70—7.30 (2H, bs, CONH₂), 7.10 [1H, s, C(3)-H], 8.30 (1H, s, pyrazole ring-H), 12.00 and 13.20 (each 1H, each bs, COOH and/or NH).

Reaction of 7a (or 7b) with Diazomethane—Compound **4a** (or **4b**) (1 mmol) was added to a solution of diazomethane in ether with stirring at room temperature. After stirring had been continued for 12 h, the resulting precipitate was collected by filtration, and recrystallized.

Methyl 4-Acetyl-1-(4-cyano-1-methylpyrazol-3-yl)-5-methylpyrrole-2-carboxylate (9a)—80.2% yield. mp 197—199°C (EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2230 (CN), 1700, 1660 (CO). NMR δ : 2.29 (3H, s, CH₃), 2.44 (3H, s, COCH₃), 3.68 (3H, s, NCH₃), 3.94 (3H, s, CO₂CH₃), 7.55 [1H, s, C(3)-H], 8.70 (1H, s, pyrazole ring-H). Anal. Calcd for C₁₄H₁₄N₄O₃: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.51; H, 4.96; N, 19.28.

Methyl 4-Acetyl-1-(4-carbamoyl-1-methylpyrazol-3-yl)-5-methylpyrrole-2-carboxylate (9b)—79.6% yield. mp 273—275°C (MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3430, 3200 (NH), 1690, 1660 (CO). NMR δ : 2.19 (3H, s,

CH₃), 2.41 (3H, s, COCH₃), 3.60 (3H, s, NCH₃), 3.88 (3H, s, CO₂CH₃), 6.80—7.40 (2H, bs, CONH₂), 7.40 [1H, s, C(3)—H], 8.30 (1H, s, pyrazole ring-H). *Anal.* Calcd for C₁₄H₁₆N₄O₄: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.00; H, 5.13; N, 18.61.

6-Acetyl-8-alkoxy-3-cyano-7,8-dihydro-4H-pyrazolo[1,5-*a*][1,3]diazepine-8-carboxylic Acids (10, 11 and 12)—A solution of KOH (1.2 mmol) in water (2 ml) was added to a solution of **3a** (or **13**) (1 mmol) in ROH (R=Me, Et, *n*-Pr) (100 ml) under ice cooling, and then the mixture was allowed to stand for 3 h (in the case of **13** for 12 h). After removal of the solvent by evaporation, the residue was dissolved in water (5 ml). The aqueous solution was acidified by the addition of conc. HCl under ice cooling. The precipitate was collected by filtration, and recrystallized (Table III).

TABLE III. Physical and Spectral Data for 8-Alkoxy-pyrazolodiazepine Derivatives

Compd. No.	mp (°C)	Yield (%)	Formula	Analyses (%) Calcd (Found)			IR(KBr) ν cm ⁻¹	
				C	H	N	CN	CO
10	140—142 (MeOH-H ₂ O) ^a	81.0	C ₁₂ H ₁₂ N ₄ O ₄ ·H ₂ O	48.98 (49.08)	4.80 4.78	19.04 18.96	2220	1750
11	115—117 (EtOH-H ₂ O) ^a	80.7	C ₁₃ H ₁₄ N ₄ O ₄ ·1/4H ₂ O	52.96 (53.09)	4.96 5.13	19.01 18.96	2220	1750
12	161—164 (AcOEt) ^a	88.4	C ₁₄ H ₁₆ N ₄ O ₄	55.25 (55.00)	5.30 5.38	18.41 18.26	2220	1760
16	71—72 (B-H) ^a	77.8	C ₁₄ H ₁₆ N ₄ O ₄ ·1/6 C ₆ H ₆	56.77 (56.61)	5.40 5.41	17.65 17.39	2220	1760 1650
17	165—166 (B-H) ^a	66.3	C ₁₅ H ₁₈ N ₄ O ₄	56.59 (56.48)	5.70 5.59	17.60 17.40	2220	1760 1650
18	160—163 (B-L) ^a	88.1	C ₁₆ H ₂₀ N ₄ O ₄	57.82 (57.70)	6.07 6.04	16.86 16.71	2220	1760 1630

Compd. No.	NMR δ (DMSO-d ₆) (J=Hz)								
	R ₁	R ₂	CO ₂ CH ₂ CH ₃ (J=6)	COCH ₃	CH ₂ (J=16)	C ₅ -H	C ₂ -H	NH	OR ₂
10	H	Me		2.28	2.75(d) 3.48(d)	7.32(bs)	7.89	10.65(bs)	3.12 (s, OCH ₃)
11	H	Et		2.28	2.78(d) 3.48(d)	7.32(bd) (J=6)	7.89	10.50(bd) (J=6)	0.92 (t, J=6, OCH ₂ CH ₃) 3.15, 3.72 (each 1H, each m, OCH ₂ CH ₃)
12	H	<i>n</i> -Pr		2.30	2.84(d) 3.51(d)	7.35(bd) (J=6)	7.89	10.72(bd) (J=6)	0.70 (t, J=6, OCH ₂ CH ₂ -CH ₃) 1.32 (m, OCH ₂ CH ₂ CH ₃) 3.03, 3.70 (each 1H, each m, OCH ₂ CH ₂ CH ₃)
16	Et	Me	1.22(3H, t) 4.24(2H, q)	2.29	2.78(d) 3.52(d)	7.36	7.91	10.62(br)	3.13 (s, OCH ₃)
17	Et	Et	1.20(3H, t) 4.21(2H, q)	2.28	2.78(d) 3.48(d)	7.30	7.89	10.78(br)	0.92 (t, J=6, OCH ₂ CH ₃) 3.15, 3.68 (each 1H, each m, OCH ₂ CH ₃)
18	Et	<i>n</i> -Pr	1.22(3H, t) 4.22(2H, q)	2.28	2.75(d) 3.52(d)	7.31	7.89	11.68(br)	0.70 (t, J=6, OCH ₂ CH ₂ -CH ₃) 1.25 (m, OCH ₂ CH ₂ CH ₃) 3.05, 3.70 (each 1H, each m, OCH ₂ CH ₂ CH ₃)

The following abbreviations are used: B=benzene, H=*n*-hexane, L=ligroin.

^a) Recrystallization solvent.

5a-Acetyl-5-alkoxy-6a-ethoxycarbonyl-4,5,5a,6a-tetrahydro-6H-cyclopropa[5a,6a]pyrazolo[1,5-a]pyrimidine-3-carbonitriles (13, 14 and 15)—A solution of **3a** (1 mmol) in ROH (R=Me, Et, *n*-Pr) (30 ml) was refluxed for 1 h. After removal of the solvent by evaporation, the residue was recrystallized from benzene (Table II).

Ethyl 6-Acetyl-8-alkoxy-3-cyano-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepine-8-carboxylates (16, 17 and 18)—A solution of **3a** (1 mmol) in ROH (R=Me, Et, *n*-Pr) (30 ml) was refluxed for 5 days. After removal of the solvent by evaporation, the residue was recrystallized (Table III).

Hydrolysis of 17—A solution of KOH (126 mg) in water (2 ml) was added to a solution of **17** (200 mg) in EtOH (50 ml), then the mixture was refluxed for 3 days. After removal of the solvent by evaporation, the residue was dissolved in water (5 ml). The aqueous solution was acidified by the addition of conc. HCl under ice cooling. The precipitate was collected by filtration to give **11** (25 mg, 13.7%), which was identified by mixed melting point determination and IR comparison with an authentic sample.

Ethyl 3-Cyano-4,6-diacetyl-7,8-dihydro-8-ethoxy-4H-pyrazolo[1,5-a][1,3]diazepine-8-carboxylate (19)—A solution of **17** (1 mmol) in acetic anhydride (10 ml) and pyridine (0.5 ml) was heated at 70°C for 2 h. After removal of excess acetic anhydride by evaporation *in vacuo*, the resulting tarry oil was extracted with hot ligroin, and the extract was cooled. The resulting colorless needles were collected by filtration to give **19** (310 mg, 86.1%) of mp 87–90°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2220 (CN), 1730, 1670, 1640 (CO). NMR δ : 1.00–1.27 (6H, m, CO₂CH₂CH₃ and OCH₂CH₃), 2.40 and 2.45 (each 3H, each s, 2×COCH₃), 3.17 (2H, bs, CH₂), 3.60 (2H, q, *J*=7 Hz, OCH₂CH₃), 4.20 (2H, q, *J*=6 Hz, CO₂CH₂CH₃), 8.07 [1H, s, C(5)-H], 8.20 [1H, s, C(2)-H]. Anal. Calcd for C₁₇H₂₀N₄O₅: C, 56.66; H, 5.59; N, 15.55. Found: C, 56.56; H, 5.65; N, 15.45.

Reaction of 11 with Water—A solution of **11** (290 mg) in water (10 ml) was refluxed for 10 min, then cooled. The resulting precipitate was collected by filtration and recrystallized from EtOH to give **20** (125 mg, 45.2%) as colorless needles of mp 275–277°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3150 (NH), 2240 (CN), 1720, 1660 (CO). NMR δ : 2.42 (3H, s, COCH₃), 7.18 [1H, d, *J*=2 Hz, C(2)-H], 7.98 [1H, d, *J*=2 Hz, C(5)-H], 8.65 (1H, s, pyrazole ring-H), 13.93 (1H, bs, NH). Anal. Calcd for C₁₁H₈N₄O₃: C, 54.10; H, 3.30; N, 22.94. Found: C, 53.92; H, 3.17; N, 22.92. The filtrate was allowed to stand in a refrigerator overnight, then the resulting precipitate was collected by filtration and recrystallized from water to give **21** (31 mg, 11.3%) of mp 223–225°C; this compound is known to exist as a mixture (3:7) of keto (**21'**) and enol (**21**) tautomers. FeCl₃-K₃[Fe(CN)₆] test: positive (dark green). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3360 (OH), 2240 (CN), 1700 (CO). NMR δ : Data for keto form (**21'**) 2.73 (s, CH₃), 4.50 (s, CH₂), 8.68 and 8.80 [each s, C(2)- and/or C(5)-H]. Data for enol form (**21**) 2.83 (s, CH₃), 6.48 (s, =CH), 8.80 [s, C(2)-H], 9.33 [s, C(5)-H]. Anal. Calcd for C₁₁H₈N₄O₃: C, 54.10; H, 3.30; N, 22.94. Found: C, 54.06; H, 3.40; N, 22.96.

Ethyl 3-Cyano-7-methyl-6-pyrazolo[1,5-a]pyrimidinepyruvate (22)—A solution of **3a** (2.72 g) in 80% aqueous dioxane (50 ml) was refluxed for 10 h. After removal of the solvent by evaporation, the residue was recrystallized from EtOH to give **22** (2.01 g, 74%) as colorless needles of mp 178–179°C; this product was identical with an authentic sample.¹⁾

Ethyl E- β -Acetoxy-3-cyano-7-methyl-6-pyrazolo[1,5-a]pyrimidineacrylate (23)—A solution of **22** (2.72 g) in acetic anhydride (10 ml) and pyridine (0.5 ml) was allowed to stand overnight. After removal of excess acetic anhydride *in vacuo*, the residue was recrystallized from EtOH to give **23** (2.46 g, 78.2%) as colorless needles of mp 151–153°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2240 (CN), 1720 (CO). NMR δ : 1.30 (3H, t, *J*=6 Hz, CO₂CH₂CH₃), 2.28 (3H, s, OCOCH₃), 2.86 (3H, s, CH₃), 4.28 (2H, q, *J*=6 Hz, CO₂CH₂CH₃), 7.64 (1H, s, =CH), 8.85 and 8.88 [each 1H, each s, C(2)- and/or C(5)-H]. Anal. Calcd for C₁₅H₁₄N₄O₄: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.42; H, 4.40; N, 18.12.

Ethyl 8-Acetoxy-6-acetyl-3-cyano-7,8-dihydro-4H-pyrazolo[1,5-a][1,3]diazepine-8-carboxylate (24)—A solution of **3a** (2.72 g) in glacial acetic acid (50 ml) was refluxed for 10 min. After removal of the solvent by evaporation, the residue was recrystallized from EtOH-H₂O to give **24** (2.08 g, 62.8%) as colorless needles of mp 180–181°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200–3000 (NH), 2240 (CN), 1760 (CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 318 (4.37), 375 (2.92). NMR δ : 1.13 (3H, t, *J*=6 Hz, CO₂CH₂CH₃), 2.08 (3H, s, OCOCH₃), 2.33 (3H, s, COCH₃), 3.30 and 3.60 (each 1H, each d, *J*=16 Hz, CH₂), 4.15 (2H, q, *J*=6 Hz, CO₂CH₂CH₃), 7.37 [1H, s, C(5)-H], 7.93 [1H, s, C(2)-H], 10.85 (1H, bs, NH). Anal. Calcd for C₁₅H₁₆N₄O₅: C, 54.21; H, 4.85; N, 16.86. Found: C, 54.14; H, 5.02; N, 16.86.

5-Acetyl-3-hydroxy-1-(4-cyanopyrazol-3-yl)-2-pyridone (25)—A solution of KOH (56 mg) in water (3 ml) was added to a solution of **24** (332 mg) in EtOH (150 ml) under ice cooling, and then the mixture was allowed to stand for 5 h. After removal of the solvent by evaporation, the residue was dissolved in water (5 ml). The aqueous solution was acidified by the addition of conc. HCl under ice cooling. The precipitate was collected by filtration and recrystallized from a mixture of dimethylsulfoxide and water to give **25** (227 mg, 93%) of mp >300°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300 (OH), 2240 (CN), 1660, 1630 (CO). NMR δ : 2.41 (3H, s, COCH₃), 7.18 [1H, d, *J*=3 Hz, C(4)-H], 8.13 [1H, d, *J*=3 Hz, C(6)-H], 8.75 (1H, s, pyrazole ring-H), 10.25 and 14.35 (each 1H, each bs, NH and/or OH). Anal. Calcd for C₁₁H₈N₄O₃: C, 54.10; H, 3.30; N, 22.94. Found: C, 53.97; H, 3.37; N, 22.66.

3-Acetoxy-5-acetyl-1-(1-acetyl-4-cyanopyrazol-3-yl)-2-pyridone (26)—A solution of **25** (244 mg) in acetic anhydride (10 ml) and pyridine (0.5 ml) was allowed to stand overnight. After removal of excess acetic anhydride by evaporation *in vacuo*, the residue was recrystallized from benzene to give **26** (200 mg,

61%) as colorless needles of mp 169–170°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2240 (CN), 1780, 1680 (CO). NMR δ : 2.30 (3H, s, OCOCH₃), 2.47 (3H, s, COCH₃), 2.73 (3H, s, NCOCH₃), 7.68 [1H, d, $J=3$ Hz, C(4)-H], 8.53 [1H, d, $J=3$ Hz, C(6)-H], 9.44 (1H, s, pyrazole ring-H). *Anal.* Calcd for C₁₅H₁₂N₄O₅: C, 54.88; H, 3.68; N, 17.07. Found: C, 54.62; H, 3.62; N, 17.26.

Ethyl 4-Acetyl-1-(4-carbamoylpyrazol-3-yl)-5-methylpyrrole-2-carboxylate (27)—A solution of **4a** (1.0 g) in acetic acid (50 ml) was refluxed for 12 h. After removal of the solvent by evaporation, the residue was recrystallized from EtOH to give **27** (289 mg, 27%) of mp 274–278°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3480, 3150, 2950 (NH), 1695, 1660, 1640 (CO). NMR δ : 1.11 (3H, t, $J=6$ Hz, CO₂CH₂CH₃), 2.18 (3H, s, CH₃), 2.42 (3H, s, COCH₃), 4.02 (2H, q, $J=6$ Hz, CO₂CH₂CH₃), 6.70–7.40 (2H, bs, CONH₂), 7.36 [1H, s, C(3)-H], 8.33 (1H, s, pyrazole ring-H), 13.42 (1H, bs, NH). *Anal.* Calcd for C₁₄H₁₆N₄O₄: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.04; H, 5.44; N, 18.23.

X-Ray Determination of 4-Acetyl-1-(4-cyanopyrazol-3-yl)-5-methylpyrrole-2-carboxylic Acid (7a)—Transparent, colorless, plate-like crystals were obtained by recrystallization from EtOH solution. Oscillation and Weissenberg photographs showed the crystal to be monoclinic and the space group to be $P2_1/c$, as judged from the systematic absence of spectral lines and the statistical intensity distributions. The cell constants were determined on a Rigaku four-circle diffractometer using 22 reflections and refined by the least-squares method as follows: $a=7.688(2)$, $b=9.124(2)$, $c=17.357(5)$ Å, $\beta=93.36(1)^\circ$ and $V=1215.4(5)$ Å³. The density of 1.408(1) g·cm⁻³, measured by the flotation method using a mixture of benzene and carbon tetrachloride, showed that four molecules are contained in a unit cell. Three-dimensional intensity data of a crystal with dimensions of $0.3 \times 0.2 \times 0.4$ mm³ were collected with the diffractometer using graphite-monochromated Cu $K\alpha$ radiation at room temperature. By means of the ω - 2θ scan technique, all the intensities of 2068 independent reflections within $\sin \theta/\lambda$ less than 0.588 Å^{-1} were collected at a rate of 4°C/min, while the background was counted for 5s at the edges of the reflections. The intensities of four standard reflections monitored at 100-reflection intervals showed no evidence of structural deterioration during data collection. Lorentz and polarization corrections were applied, but no absorption correction was made because of the small crystal size.

The structure was solved by the direct method with the computer program, MULTAN78,¹¹⁾ using 176 reflections with $|E| \geq 1.75$. A set of the highest combined figure of merit was used for an E map calculation,

TABLE IV. Atomic Coordinates of **7a** with Their Estimated Standard Deviations

Atom	x	y	z
C (1)	0.3690(3)	-0.2138(2)	0.0751(1)
C (2)	0.2626(3)	-0.1804(2)	0.0090(1)
C (2)	0.3792(3)	-0.1530(2)	-0.0469(1)
N (4)	0.5373(2)	-0.1727(2)	-0.0130(1)
N (5)	0.5360(2)	-0.2102(2)	0.0621(1)
N (6)	0.3152(2)	-0.2554(2)	0.1489(1)
C (7)	0.3014(3)	-0.3970(2)	0.1722(1)
C (8)	0.2475(3)	-0.3949(2)	0.2475(1)
C (9)	0.2299(3)	-0.2462(2)	0.2691(1)
C (10)	0.2715(3)	-0.1614(2)	0.2086(1)
C (11)	0.0781(3)	-0.1807(3)	0.0017(1)
N (12)	-0.0705(3)	-0.1865(3)	-0.0036(1)
C (13)	0.3371(3)	-0.5225(3)	0.1205(1)
C (14)	0.2152(3)	-0.5226(3)	0.2947(1)
O (15)	0.2363(3)	-0.6466(2)	0.2700(1)
C (16)	0.1558(4)	-0.4991(3)	0.3738(2)
C (17)	0.2760(3)	-0.0020(2)	0.2025(1)
O (18)	0.3160(3)	0.0657(2)	0.1467(1)
O (19)	0.2299(3)	0.0612(2)	0.2668(1)
H (3)	0.357(3)	-0.119(3)	-0.102(2)
H (4)	0.646(3)	-0.162(3)	-0.036(2)
H (9)	0.194(3)	-0.208(3)	0.320(1)
H (13a)	0.394(4)	-0.494(4)	0.084(2)
H (13b)	0.230(5)	-0.574(4)	0.101(2)
H (13c)	0.412(5)	-0.596(4)	0.150(2)
H (16a)	0.058(4)	-0.432(3)	0.374(2)
H (16b)	0.249(4)	-0.452(4)	0.408(2)
H (16c)	0.118(4)	-0.591(4)	0.393(2)
H (19)	0.232(4)	0.164(4)	0.263(2)

Fig. 3. Bond Lengths and Angles of the Molecule of 7a

and the positions of all the 17 nonhydrogen atoms were reasonably obtained. Isotropic refinement using the full-matrix least-squares method converged to give an R value of 0.141. Anisotropic refinement was then performed by the block-diagonal least-squares method. All the hydrogen atoms were found from a difference Fourier synthesis at the stage of $R=0.077$. After inclusion of the hydrogen atoms with isotropic thermal parameters, further refinement was carried out. The final least-squares refinement was computed with a weighting scheme of the following form: $w=0.42$ for $F_o=0.0$, $w=1.0$ for $0<F_o<17.0$ and $w=1.0/[1.0+0.227(F_o-17.0)]$ for $F_o>17.0$. During the last cycle of refinement, none of the positional parameters shifted by more than one-fifth of the estimated standard deviation. The final R value was 0.056. The final positional parameters with their estimated standard deviations are listed in Table IV. Bond lengths and angles for nonhydrogen atoms, with the atomic numbering, are given in Fig. 3.¹²⁾ The atomic scattering factors for all atoms were taken from International Tables for X-ray Crystallography.¹³⁾ All numerical calculations were carried out on an ACOS-700 computer at the Computation Center of Osaka University using programs of The Universal Crystallographic Computing System.¹⁴⁾

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