Ring Transformation of 6*H*-Cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine. IV (1). Reduction and Reaction of 5a-Acetyl-6a-ethoxycarbonyl-5a,6a-dihydro-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles with Primary Amines

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The reaction of 5a-acetyl-6-ethoxycarbonyl-5a,6a-dihydro-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**1a**) with benzylamine gave ethyl 1-benzyl-5-cyano-8a,9-dihydro-2-methyl-1*H*-pyrrolo[3,4-*e*]-pyrazolo[1,5-*a*]pyrimidine-8a-carboxylate (**2a**), in addition to 5-acetyl-3-benzylamino-1-(4-cyanopyrazol-3-yl)-2-pyridone (**3**). Reaction of **1a** with aniline gave ethyl 6-acetyl-8-anilino-3-cyano-7,8-dihydro-4*H*-pyrazolo-[1,5-*a*][1,3]diazepine-8-carboxylate (**4**), in addition to ethyl 3-cyano-7-methyl-6-pyrazolo[1,5-*a*]pyrimidine-acrylate (**5**). On the other hand, the same reactions of **1b** with benzylamine or aniline gave **2b** or **8b**, respectively.

Though catalytic hydrogenation of **1a** over 5% palladium-carbon proceeded by ring fission of cyclopropane ring to give **9**, **1a** (or **1b**) afforded 4,5-dihydro derivatives (**13** or **15**) by catalytic hydrogenation over platinum oxide.

The reactivity of 5-methoxy-4,5,5a,6a-tetrahydro-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine (**16**), which are related analogs of **1a,b**, is also described.

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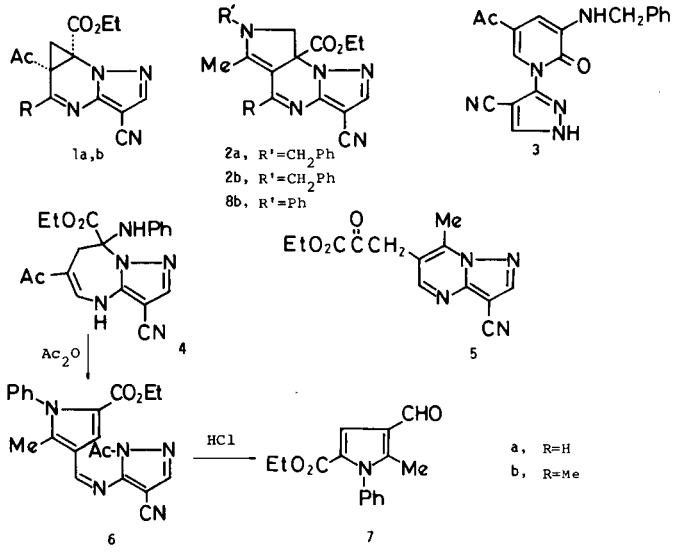
Recently we reported the reaction of 5a-acetyl-6a-ethoxycarbonyl-5a,6a-dihydro-6*H*-cyclopropa[*e*]pyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (**1a**) and its 5-methyl derivatives (**1b**) with *N*-methylaniline, and it was concluded that **1a** is much more subject to ring fission of the cyclopropane ring than that of **1b** to yield the ring transformed products such as ethyl *E*- and *Z*-β-*N*-methylanilino-6-pyrazolo[1,5-*a*]pyrimidineacrylates, *N*-pyrazolylpyrrole, and *N*-pyrazolylpyridone (2). In this paper we wish to report the reaction of **1a** and **1b** with primary amines as well as their catalytic hydrogenation.

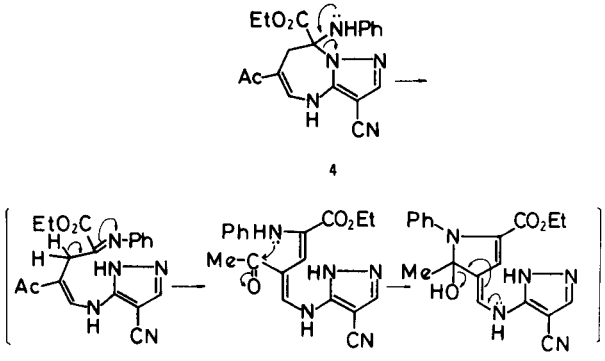
Treatment of **1a** with benzylamine in refluxing benzene gave ethyl 1-benzyl-5-cyano-8a,9-dihydro-2-methyl-1*H*-pyrrolo[3,4-*e*]pyrazolo[1,5-*a*]pyrimidine-8a-carboxylate (**2a**) in 31.7% yield, in addition to 7.8% of compound **3**. The structural assignment of **2a** was made on the basis of the results of elemental analyses and the spectral data detailed in the experimental section. Formation of the product **2a** can be explained by the nucleophilic attack of benzylamine at C(6) of **1a** followed by dehydrative cyclization with acetyl carbonyl carbon atom. The structure of another product **3** with the empirical formula $C_{18}H_{15}N_5O_2$ was supported by the spectral data; the infrared (ir) spectrum showed carbonyl absorption bands at 1680 and 1660 cm^{-1}, and the proton magnetic resonance (pmr) spectrum showed no $-CO_2CH_2CH_3$ group and exhibited a pair of doublet (J = 2 Hz) at 6.53 ppm and 7.90 ppm due to C(4)-and C(6)-protons as well as a singlet at 8.78 pm due to C(5')-proton. On the basis of these results, the structure of **3** was determined as 5-acetyl-3-benzylamino-1-(4-cyanopyrazol-3-yl)-2-pyridone. The ring transformation of **1a** into *N*-pyrazolylpyridone (**3**) can be similarly explained by initial nucleophilic attack of benzylamine at C(6a) of **1a** as shown in the previous report (2). Similarly reaction of **1b** with benzylamine gave **2b** in 62.5% yield. On the other hand, when **1a** was heated with aniline in benzene for 30 minutes, ethyl 6-acetyl-8-anilino-3-cyano-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepine-8-carboxylate (**4**) in 45.7% yield, in addition to 11.4% yield of compound **5** (1). The structure of **4** was proven by its elemental analysis and by spectroscopic methods. In particular, the C(7)-methylene protons appeared at 3.07 ppm as broad singlet in the pmr

Scheme I



spectrum. The product **5** may be obtained by hydrolysis of the intermediate β-anilino-3-cyano-7-methyl-6-pyrazolo-[1,5-*a*]pyrimidineacrylate (3), which was formed *via* ring transformation of **4** (2). An attempt to synthesize the corresponding acetate of **4** by treatment with acetic anhydride failed, but ethyl 4-(2-acetyl-4-cyano-3-pyrazole-iminomethyl)-5-methyl-1-phenylpyrole-2-carboxylate (**6**) was isolated. As detailed in the exprimental section, the spectral data are fully consistent with the structure **6**. This assignment was further supported by the hydrolysis of **6** to give pyrrole-3-carboxaldehyde (**7**). To account for this ring transformation of **4** to **6**, the mechanism shown in Scheme II was considered. Then, the reaction of **1b** with aniline

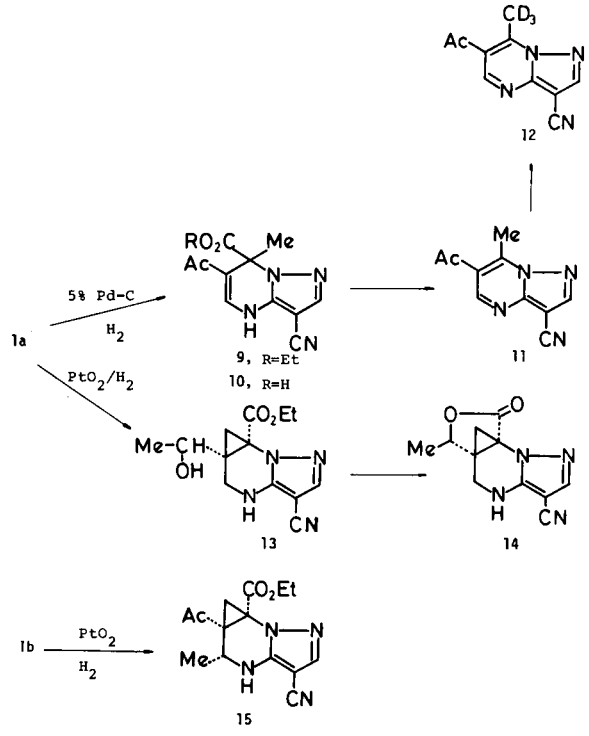
Scheme II



was carried out by refluxing it in xylene to give **8b** in 17.3% yield, since no reaction takes place in refluxing benzene in this case.

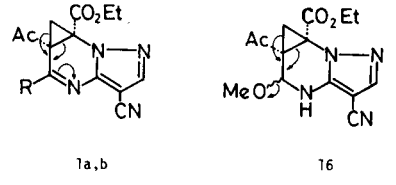
Next, catalytic hydrogenation of **1a,b** was investigated. Thus catalytic hydrogenation of **1a** in the presence of 5% palladium carbon as catalyst gave ethyl 6-acetyl-3-cyano-4,7-dihydro-7-methylpyrazolo[1,5-*a*]pyrimidine-7-carboxylate (**9**) in 51.6% yield. However, **1b** resulted in the recovery of the starting material under the same conditions. Treatment of **9** with potassium hydroxide gave the carboxylic acid **10**, which was then oxidized with manganase dioxide in dimethylformamide (DMF) to yield 6-acetyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**11**). The pmr spectrum of **11** in deuteriodimethylsulfoxide (DMSO-d_6) showed two methyl signals at 2.73 ppm and 3.03 ppm. Interestingly, it was found that a signal of 3.03 ppm disappears readily by treatment with deuterium oxide. Thus, compound **11** was treated with deuterium oxide in DMSO to give the trideuteriomethyl derivative **12**, whose mass spectrum showed a molecular ion peak at m/z 203 and a fragment ion peak at m/z: 160 (M^+-$COCH_3$). From these results, the structure of **12** was established as the 7-trideuteriomethyl derivative. On the other hand, catalytic hydrogenation of **1a,b** over platinum oxide as the catalyst afforded the 4,5-dihydro-5a-(α-hydroxy)ethyl derivative **13** from **1a** and the 4,5-dihydro derivative **15** from **1b** in 61% and quantitative yields, respectively. Compound **13**, upon refluxing in xylene, was transformed into the lactone **14** in quantitative yield. The stereostructure of **15** was determined as shown in Scheme III based upon pmr spectral data which exhibited a signal due to the C(5)-methyl protons as a doublet at 1.50 ppm and the C(5)-proton as a quartet at 3.50 ppm (4). Based on these results, it may be concluded that the ring fission of the

Scheme III



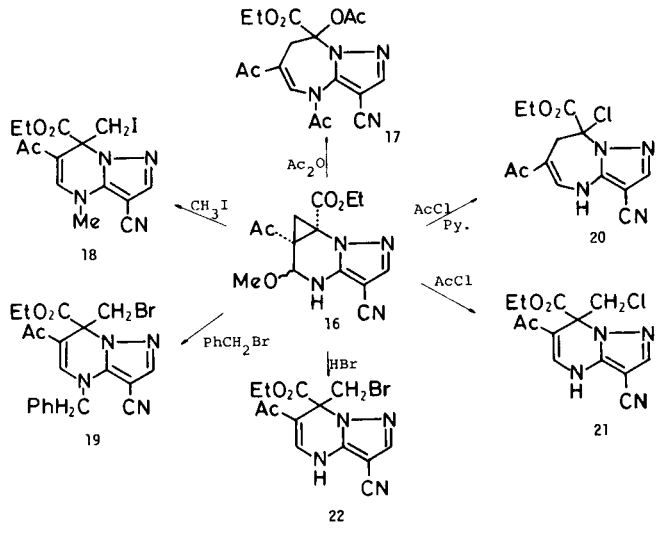
cyclopropane ring is strongly affected by the presence of C(5)=N double bond as shown in Scheme IV.

Scheme IV



Previously, we reported (5) that **1a** gave a mixture of *cis* and *trans* isomers of 5a-acetyl-6a-ethoxycarbonyl-5-methoxy-4,5,5a,6a-tetrahydro-6*H*-cyclopropa[*e*]pyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (**16**) by refluxing it in methanol. Since the presence of the C(5)-methoxy group as the leaving group is considered to affect the ring fission of the cyclopropane ring of **16** as shown in Scheme IV, we then investigated the reactivity of **16**. When compound **16** was refluxed in acetic anhydride, an oily substance was obtained. Purification by silica gel column chromatography gave ethyl 8-acetoxy-3-cyano-4,6-diacetyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepine-8-carboxylate (**17**) in 69%

SCHEME V



yield. Compound **16** was refluxed with methyl iodide or benzyl bromide in the presence of potassium carbonate in acetone to give 4-alkyl-4,7-dihydro-7-halomethylpyrazolo-[1,5-*a*]pyrimidines (**18** or **19**) in 73.4% and 31.9% yields, respectively. Compound **16** was then allowed to react with acetyl chloride in benzene in the presence or absence of pyridine to give 8-chloro-7,8-dihydro-4*H*-pyrazolo[1,5-*a*]-[1,3]diazepine (**20**) or 7-chloromethyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidine (**21**) in 75.7% and 13.8% yields. Compound **16** was, on treatment with 48% hydrobromic acid in methanol, also transformed into 7-bromomethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine (**22**) in 59.6% yield. The structure of these products (**17-22**) was established by the results of their elemental analyses and their spectral data detailed in the experimental section. In particular, the CH_2 protons of the diazepine ring of **17** and **20** resonated at higher field than the CH_2X (X = Cl or Br) protons of **18, 19, 21** and **22** in the pmr spectra.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra (potassium bromide unless otherwise noted) were recorded with a JASCO model IRA-1 spectrophotometer. The pmr spectra were recorded in deuteriodimethylsulfoxide (unless otherwise noted) with a Hitachi R-24A spectrometer with tetramethylsilane as an internal standard. The mass spectra were recorded with a Hitachi RMU-7L spectrometer.

Reaction of **1a** with Benzylamine.

A solution of 1 g of **1a** and 433 mg of benzylamine in 50 ml of benzene was refluxed for 30 minutes, then cooled. The resulting precipitate was collected by filtration. From the slightly soluble part in methanol was obtained 96 mg (7.8%) of 5-acetyl-3-benzylamino-1-(4-cyanopyrazol-3-yl)-2-pyridone (**3**), which was recrystallized from methanol, as colorless needles of mp 278-280°; ir: ν cm^{-1} 3430, 3300 (NH), 2220 (CN), 1680, 1660 (CO); uv (ethanol): nm λ max (log ϵ) 234 (4.29), 372 (4.12); pmr: δ 2.35 (3H, s, $COCH_3$), 4.40 (2H, d, J = 5 Hz, $NHCH_2$), 6.53 [1H, d, J = 2 Hz, C(4)-H], 6.60 (1H, t, J = 5 Hz, NH), 7.35 (5H, s, Ar-H), 7.90 [1H, d, J = 2 Hz, C(6)-H], 8.78 [1H, s, C(5')-H]; ms: m/z 333 (M^+).

Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.85; H, 4.54; N, 21.01. Found: C, 64.79; H, 4.54; N, 21.18.

From the soluble part in methanol was obtained 421 mg (31.7%) of ethyl 1-benzyl-5-cyano-8a,9-dihydro-2-methyl-1*H*-pyrrolo[3,4-*e*]pyrazolo-[1,5-*a*]pyrimidine-8a-carboxylate (**2a**), which was recrystallized from ethanol, as yellow needles of mp 184-185°; ir: ν cm^{-1} 2220 (CN), 1730 (CO); uv (ethanol): nm λ max (log ϵ) 240 (4.11), 320 (3.80) (sh), 463 (4.32); pmr: δ 1.03 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.33 (3H, s, CH_3), 4.00 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 4.40 (2H, q, J = 12 Hz, CH_2), 4.70 (2H, q, J = 16 Hz, NCH_2), 7.37 (5H, a, Ar-H), 7.85 [1H, s, C(6)-H], 8.10 (1H, s, C(3)-H]; ms: m/z 361 (M^+).

Anal. Calcd. for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.66; H, 5.29; N, 19.20.

Reaction of **1b** with Benzylamine.

A solution of 1 g of **1b** and 412 mg of benzylamine in 80 ml of benzene was refluxed for 4 hours. After removal of the solvent by evaporation, the residue was recrystallized from ethanol to give 820 mg (62.5%) of ethyl 1-benzyl-5-cyano-8a,9-dihydro-2,3-dimethyl-1*H*-pyrrolo[3,4-*e*]pyrazolo-[1,5-*a*]pyrimidine-8a-carboxylate (**2b**) as yellow needles of mp 159-160°; ir: ν cm^{-1} 2220 (CN), 1730 (CO); pmr δ 1.03 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.35 (6H, s, 2 × CH_3), 4.00 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 4.30 (2H, q, J = 12 Hz, CH_2), 4.65 (2H, q, J = 12 Hz, NCH_2), 7.32 (5H, s, Ar-H), 7.80 [1H, s, C(6)-H].

Anal. Calcd. for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.66. Found: C, 66.89; H, 5.82; N, 18.51.

Reaction of **1a** with Aniline.

A solution of 1 g of **1a** and 375 mg of aniline in 50 ml of benzene was refluxed for 30 minutes, then cooled. The resulting precipitate was collected by filtration and purified by recrystallization from ethanol to give 614 mg (45.7%) of ethyl 6-acetyl-8-anilino-3-cyano-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepine-8-carboxylate (**4**) as colorless needles of mp 152-153°; ir: ν cm^{-1} 3400, 3140 (NH), 2220 (CN), 1750 (CO); pmr δ 1.14 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.26 (3H, s, $COCH_3$), 3.07 (2H, bs, CH_2), 4.23 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 6.01 (1H, s, NH), 6.55-7.25 (5H, m, Ar-H), 8.13 [1H, s, C(5)-H], 8.37 [1H, s, C(2)-H], 13.41 (1H, bs, NH).

Anal. Calcd. for $C_{19}H_{19}N_5O_3$: C, 62.45; H, 5.24; N, 19.17. Found: C, 62.49; H, 5.15; N, 19.19.

The filtrate was concentrated *in vacuo*, and the residue was recrystallized from ethanol to give 114 mg (11.4%) of ethyl 3-cyano-7-methyl-6-pyrazolo[1,5-*a*]pyrimidineacrylate (**5**) of mp 178-179°, which was identical with an authentic sample (1) in all respects.

Reaction of **1b** with Aniline.

A solution of 1 g of **1b** and 365 mg of aniline in 50 ml of xylene was refluxed for 16 hours. After removal of the solvent by evaporation, the residue was recrystallized from ethanol to give 218 mg (17.3%) of ethyl 5-cyano-8a,9-dihydro-2,3-dimethyl-1-phenyl-1*H*-pyrrolo[3,4-*e*]pyrazolo-[1,5-*a*]pyrimidine-8a-carboxylate (**8b**) as yellow needles of mp 172-173°; ir: ν cm^{-1} 2220 (CN), 1720 (CO); pmr: δ 1.10 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.28 and 2.44 (each 3H, each s, 2 × CH_3), 4.10 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 4.85 (2H, q, J = 12 Hz, CH_2), 7.30-7.60 (5H, m, Ar-H), 7.94 [1H, s, C(2)-H].

Anal. Calcd. for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.31; H, 5.40; N, 19.62.

Ethyl 4-(2-Acetyl-4-cyano-3-pyrazoleiminomethyl)-5-methyl-1-phenylpyrrole-2-carboxylate (**6**).

A drop of pyridine was added to a solution of 1.47 g of **4** in 5 ml of acetic anhydride, and the mixture was heated at 80° for 18 hours. After removal of acetic anhydride by evaporation, the residue was dissolved in chloroform. The chloroform solution was washed with saturated sodium bicarbonate solution, water, and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with chloroform gave 198 mg (50.8%) of **6** as

colorless needles (from ethanol) of mp 163-165°; ir: ν cm^{-1} 2220 (CN), 1750, 1690 (CO); pmr: δ 1.10 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.28 (3H, s, CH_3), 2.68 (3H, s, $COCH_3$), 4.03 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 7.20-7.60 (5H, m, Ar-H), 7.45 (1H, s, pyrrole ring-H), 9.00 (1H, s, pyrazole ring-H), 9.18 (1H, s, CH).

Anal. Calcd. for $C_{21}H_{19}N_5O_3$: C, 64.77; H, 4.92; N, 17.99. Found: C, 64.61; H, 5.08; N, 17.93.

5-Ethoxycarbonyl-2-methyl-1-phenylpyrrole-3-carboxaldehyde (**7**).

A solution of 365 mg of **6** and a drop of concentrated hydrochloric acid in 10 ml of ethanol was refluxed for 1 hour. After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with chloroform gave 225 mg (87.5%) of **7** as an oil; ir (chloroform): ν cm^{-1} 1700, 1660 (CO); pmr (deuteriochloroform): δ 1.16 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.31 (3H, s, CH_3), 4.12 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 7.10-7.50 (5H, m, Ar-H), 7.46 [1H, s, C(4)-H], 9.60 (1H, s, CHO); ms: m/z 257 (M^+).

Ethyl 6-Acetyl-3-cyano-4,7-dihydro-7-methylpyrazolo[1,5-*a*]pyrimidine-7-carboxylate (**9**).

A solution of 500 mg of **1a** in 50 ml of dioxane was shaken with hydrogen over 0.3 g of 5% palladium-carbon for 4 hours using a Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo* to afford 260 mg (51.6%) of **9** as colorless needles of mp 222-223°, which were recrystallized from benzene; ir: ν cm^{-1}: 3240 (NH), 2220 (CN), 1750, 1630 (CO); pmr: δ 1.06 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 1.70 (3H, s, CH_3), 2.26 (3H, s, $COCH_3$), 4.05 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 7.72 [1H, s, C(5)-H], 7.95 [1H, s, C(2)-H], 11.46 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.81; H, 5.15; N, 20.16.

6-Acetyl-3-cyano-4,7-dihydro-7-methylpyrazolo[1,5-*a*]pyrimidine-7-carboxylic Acid (**10**).

A solution of 135 mg of potassium hydroxide in 2 ml of water was added to a solution of 274 mg of **9** in 20 ml of ethanol, then the mixture was refluxed for 10 hours. After removal of the solvent by evaporation, the residue was dissolved in 5 ml of water. The aqueous solution was acidified by the addition of concentrated hydrochloric acid under ice cooling. The precipitate was collected by filtration and recrystallized from water to give 101 mg (41.1%) of **10** as colorless needles of mp 270-271°; ir: ν cm^{-1} 3600-3000 (COOH and NH), 2220 (CN), 1740, 1630 (CO); pmr: δ 1.70 (3H, s, CH_3), 2.26 (3H, s, $COCH_3$), 7.66 [1H, s, C(5)-H], 7.92 [1H, s, C(2)-H], 11.41 (1H, bs, NH), 12.50-13.00 (1H, br, COOH).

Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.76. Found: C, 53.60; H, 4.20; N, 22.69.

6-Acetyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**11**).

A suspension of 246 mg of **10** and 423 mg of manganese dioxide in 50 ml of methanol was stirred for 7 hours at room temperature. Manganese dioxide was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was recrystallized from ethanol to give 137 mg (68.5%) of **11** as colorless needles of mp 178-179°; ir: ν cm^{-1} 2220 (CN), 1690 (CO); pmr: δ 2.73 (3H, s, $COCH_3$), 3.03 (3H, s, CH_3), 8.95 (1H, s, C(2)-H], 9.25 [1H, s, C(5)-H]; ms: m/z 200 (M^+), 183 (M^+-15), 157 (M^+-43).

Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99.Found: C, 59.70; H, 4.14; N, 28.08.

6-Acetyl-7-trideuteriomethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**12**).

A solution of 100 mg of **11** and ten drops of deuterium oxide in 5 ml of DMSO was heated at 70-80° for 5 minutes, then cooled. The resulting needles were collected by filtration and recrystallized from ethanol to give 75 mg of **12** of mp 178-179°; pmr: δ 2.73 (3H, s, $COCH_3$), 8.97 [1H, s, C(2)-H], 9.28 [1H, s, C(5)-H]; ms: m/z 203 (M^+), 188 (M^+-15), 160 (M^+-43).

Anal. Calcd. for $C_{10}H_5D_3N_4O$: C, 59.09; N, 27.57. Found: C, 59.34; N, 27.52.

Ethyl 3-Cyano-5a-(α-hydroxy)ethyl-4,5,5a,6a-tetrahydro-6*H*-cyclopropa[*e*]-pyrazolo[1,5-*a*]pyrimidine-6a-carboxylate (**13**).

A solution of 500 mg of **1a** in 50 ml of dioxane was shaken with hydrogen over 0.15 g of platinum oxide for 4 hours using a Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo* to afford 310 mg (61.0%) of **13** as colorless needles of mp 209-210°, which were recrystallized from ethyl acetate; ir: ν cm^{-1} 3330 (OH), 2220 (CN), 1730 (CO); pmr: δ 1.00-1.40 [7H, m, $CO_2CH_2CH_3$, CH_3 and C(6)-H], 1.70 [1H, d, J = 6 Hz, C(6)-H], 3.43 (1H, q, J = 6 Hz, $CHCH_3$), 3.48 (2H, q, J = 12 Hz, CH_2), 4.18 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 4.90 (1H, d, J = 6 Hz, OH), 7.64 [2H, s, C(2)-H and NH].

Anal. Calcd. for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.22; H, 5.97; N, 19.99.

3-Cyano-5a-(α-hydroxy)ethyl-4,5,5a,6a-tetrahydro-6*H*-cyclopropa[*e*]-pyrazolo[1,5-*a*]pyrimidine-6a-carboxylic Acid Lactone (**14**).

A solution of 276 mg of **13** in 30 ml of xylene was refluxed for 24 hours. After removal of the solvent by evaporation, the residue was recrystallized from ethanol to give 230 mg (100%) of **14** of mp 298-300°; ir: ν cm^{-1} 3280 (NH), 2220 (CN), 1780 (CO); pmr: δ 1.46 (3H, d, J = 6 Hz, $CHCH_3$), 1.88 (2H, s, CH_2), 3.56 (2H, q, J = 12 Hz, CH_2), 4.70 (1H, q, J = 6 Hz, CH), 7.60 (1H, bs, NH), 7.73 [1H, s, C(2)-H].

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.20; H, 4.63; N, 24.34.

Ethyl 5a-Acetyl-3-cyano-5-methyl-4,5,5a,6a-tetrahydro-6*H*-cyclopropa[*e*]-pyrazolo[1,5-*a*]pyrimidine-6a-carboxylate (**15**).

A solution of 500 mg of **1b** in 50 ml of dioxane was shaken with hydrogen over 0.15 g of paltinum oxide for 24 hours using a Skita apparatus. The reaction mixture was filtered, and concentrated *in vacuo* to afford 504 mg (100%) of **15** as colorless needles of mp 143-145°, which were recrystallized from ethanol; ir: ν cm^{-1} 3300 (OH and/or NH), 2220 (CN), 1740, 1710 (CO); pmr: δ 1.16 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 1.32 (3H, d, J = 6 Hz, $CHCH_3$), 1.72 and 2.16 (each 1H, each d, J = 6 Hz, CH_2), 3.75 (1H, q, J = 6 Hz, $CHCH_3$), 4.15 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 7.75 [1H, s, C(2)-H],7.90 (1H, s, NH).

Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.44. Found: C, 58.37; H, 5.47; N, 19.40.

Ethyl 8-Acetoxy-3-cyano-4,6-diacetyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*]-[1,3]diazepine-8-carboxylate (**17**).

A solution of 304 mg of **16** in 5 ml of acetic anhydride was refluxed for 5 hours. After removal of excess acetic anhydride *in vacuo*, the residue was subjected to silica gel column chromatography. Elution with chloroform afforded 258 mg (69%) of **17** as colorless needles (from benzene-ligroin) of mp 96-100°; ir: ν cm^{-1} 2220 (CN), 1760, 1740, 1720, 1670 (CO); pmr: δ 1.18 (3H, s, $CO_2CH_2CH_3$), 2.13, 2.40 and 2.54 (each 3H, each s, 3 × $COCH_3$), 3.29 (2H, q, J = 12 Hz, CH_2), 4.25 (2H, q, J= 6 Hz, $CO_2CH_2CH_3$), 8.09 [1H, s, C(5)-H], 8.20 [1H, s, C(2)-H].

Anal. Calcd. for $C_{17}H_{18}N_4O_3 \cdot \frac{1}{2}C_6H_6$: C, 58.10; H, 5.12; N, 13.55. Found: C, 58.00; H, 5.02; N, 13.43.

Ethyl 6-Acetyl-3-cyano-4,7-dihydro-7-iodomethyl-4-methylpyrazolo-[1,5-*a*]pyrimidine-7-carboxylate (**18**).

Two hundred mg of anhydrous potassium carbonate were added to a solution of 304 mg of **16** and 1 ml of methyl iodide in 50 ml of acetone, and the mixture was refluxed for 24 hours. After the resulting solid was removed by filtration, the filtrate was condensed *in vacuo*. The residue was recrystallized from ethanol to give 304 mg (73.4%) of **18** as colorless needles of mp 178-179° ir: ν cm^{-1} 2220 (CN), 1740 (CO); pmr: δ 1.25 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.32 (3H, s, $COCH_3$), 3.70 (3H, s, NCH_3), 4.10-4.50 (4H, m, CH_2I and $CO_2CH_2CH_3$), 7.29 [1H, s, C(5)-H], 7.72 [1H, s, C(2)-H].

Anal. Calcd. for $C_{14}H_{15}IN_4O_3$: C, 40.59; H, 3.65; N, 13.53. Found: C, 40.83; H, 3.76; N, 13.77.

Ethyl 6-Acetyl-4-benzyl-7-bromomethyl-3-cyano-4,7-dihydropyrazolo-[1,5-*a*]pyrimidine-7-carboxylate (**19**).

Two hundred mg of anhydrous potassium carbonate was added to a solution of 304 mg of **16** and 0.5 ml of benzyl bromide in 50 ml of

acetone, and the mixture was refluxed for 7 hours. After the resulting solid was removed by filtration, the filtrate was condensed *in vacuo*. The residue was recrystallized from ethanol to give 141 mg (31.9%) of **19** as colorless needles of mp 165-167°; ir: ν cm^{-1} 2220 (CN), 1740, 1640 (CO); pmr (deuteriochloroform): δ 1.26 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.28 (3H, s, $COCH_3$), 4.15-4.65 (4H, m, CH_2Br and $CO_2CH_2CH_3$), 5.20 (2H, q, J = 15 Hz, NCH_2), 7.40 [6H, s, Ar-H and C(5)-H], 7.71 [1H, s, C(2)-H].

Anal. Calcd. for $C_{20}H_{19}BrN_4O_3$: C, 54.91; H, 4.32; N, 12.64. Found: C, 54.08; H, 4.37; N, 12.66.

Ethyl 6-Acetyl-8-chloro-3-cyano-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]-diazepine-8-carboxylate (**20**).

Three drops of pyridine were added to a solution of 304 mg of **16** and 3 ml of acetyl chloride in 50 ml of benzene, and the mixture was refluxed for 3 hours. After removal of the solvent by evaporation, the residue was recrystallized from benzene to give 233 mg (75.7%) of **20** as colorless needles of mp 179-180°; ir: ν cm^{-1} 3240 (NH), 2220 (CN), 1740, 1610 (CO); pmr (deuteriochloroform): δ 1.32 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.38 (3H, s, $COCH_3$), 3.64 (2H, q, J = 15 Hz, CH_2), 4.34 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 7.28 [1H, d, J = 6 Hz, C(5)-H], 7.50 [1H, s, C(2)-H], 8.65 [1H, d, J = 6 Hz, NH]; ms: m/z 272 (M^+-37).

Anal. Calcd. for $C_{13}H_{13}ClN_4O_3 \cdot \frac{1}{2}C_6H_6$: C, 51.43; H, 4.32; N, 17.78. Found: C, 51.59; H, 4.18; N, 18.00.

Ethyl 6-Acetyl-7-chloromethyl-3-cyano-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-7-carboxylate (**21**).

A solution of 304 mg of **16** and 1 ml of acetyl chloride in 50 ml of benzene was refluxed for 5 hours. After removal of the solvent by evaporation, the residue was recrystallized from ethanol to give 43 mg (13.8%) of **21** as colorless needles of mp 274-276°; ir: ν cm^{-1} 3200 (NH), 2220 (CN), 1740, 1620 (CO); ppm: δ 1.10 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.32 (3H, s, $COCH_3$), 4.13 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 4.37 (2H, q, J = 10 Hz, CH_2), 8.00 and 8.05 [each 1H, each s, C(2)-H and/or C(5)-H]; ms: m/z 309 (M^+)

Anal. Calcd. for $C_{13}H_{13}ClN_4O_3$: C, 50.57; H, 4.24; N, 18.00. Found: C, 50.59; H, 4.24; N, 17.89.

Ethyl 6-Acetyl-7-bromomethyl-3-cyano-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-7-carboxylate (**22**).

A solution of 304 mg of **16** and 1 ml of 48% hydrobromic acid in 50 ml of ethanol was refluxed for 24 hours. After removal of the solvent by evaporation, the residue was recrystallized from methanol to give 87 mg (25.0%) of **22** as colorless needles of mp 269-270°; ir: ν cm^{-1} 3240 (NH), 2220 (CN), 1740, 1620 (CO); pmr: δ 1.10 (3H, t, J = 6 Hz, $CO_2CH_2CH_3$), 2.30 (3H, s, $COCH_3$), 4.10 (2H, q, J = 6 Hz, $CO_2CH_2CH_3$), 4.38 (2H, q, J = 10 Hz, CH_2), 7.97 [1H, s, C(5)-H], 8.02 [1H, s, C(2)-H], 11.88 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{13}BrN_4O_3$: C, 44.20; H, 3.70; N, 15.86. Found: C, 44.07; H, 3.73; N, 15.91.

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REFERENCES AND NOTES

(1) Part III: T. Kurihara, T. Tani, K. Nasu, M. Inoue and T. Ishida, *Chem. Pharm. Bull.*, **29**, 3214 (1981).

(2) T. Kurihara, T. Tani and K. Nasu, *ibid.*, **29**, 1548 (1981).

(3) As shown in the previous paper (2), ethyl *E*- and *Z*-β-*N*-methylanilino-3-cyano-7-methyl-6-pyrazolo[1,5-*a*]pyrimidineacrylates have been isolated.

(4) T. Kurihara, T. Tani, H. Imai and K. Nasu, *Chem. Pharm. Bull.*, **28**, 1972 (1980).

(5) T. Kurihara, T. Tani and K. Nasu, *Heterocycles*, **15**, 265 (1981).