Ring Transformation of 6*H*-Cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine. VI [1]. Substituent Effect of 6-Substituted 5a-Acetyl-6a-ethoxycarbonyl-5a,6a-dihydro-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles

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Synthesis and reactivity of 6-ethoxycarbonyl-, 6-phenyl- and 6-methyl-5a-acetyl-6a-ethoxycarbonyl-5a,6a-dihydro-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles **4**, **5**, and **7** are described.

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In the previous papers [2], we reported the ring transformations of 5a-acetyl-6a-ethoxycarbonyl-5a,6a-dihydro-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles **2** and **3**. For examples, **2** reacted with acetic acid, potassium hydroxide as well as aliphatic or aromatic amines to give the ring transformed products, such as *N*-pyrazolylpyrole or *N*-pyrazolylpyridone derivatives. The formation of these products can be explained by the attack of nucleophiles at C(6)- or C(6a)-positions of **2**. In this paper we extended our studies to the compounds having ethoxycarbonyl, phenyl and methyl groups at C(6)-position of **2** in order to investigate their reactivity with nucleophiles.

Synthesis.

Reaction of 6-acetyl-7-ethoxycarbonylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**1**) with diazomethane giving **2** and **3** has been studied [3]. It is well known that reaction of an aromatic double bond with ethyl diazoacetate is catalyzed by copper powder. Compound **1** reacted with ethyl diazoacetate in the presence of copper powder in dioxane to yield **4** in 46% yield, together with another two products [3]. Recently it was found that, by refluxing in benzene with ethyl diazoacetate without catalyst, **1** gave **4** in 94% yield.

Treatment of **1** with phenyldiazomethane [4] in petroleum ether under ice-cooling gave a mixture of **5** and **6** in 85% and 8% yield, respectively. The structure of compound **5** was readily determined by elemental analysis and comparison of the spectral data with those of **4**. The nmr spectrum of the minor product **6** revealed the presence of two phenylcyclopropane rings; namely signals due to cyclopropane ring protons appeared at δ 4.06 and 6.46 ppm as a singlet, respectively. Further additional signals at δ 7.55 and 8.03 ppm attributable to C(2)- and C(5)-protons were observed as each singlet. Thus, 6 was confirmed to be 5a-acetyl-3,6-diphenyl-6a-ethoxycarbonyl-2a,3a,5a,6a-tetrahydro-3*H*,6*H*-dicyclopropa[*c*,*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile.

Chart 1

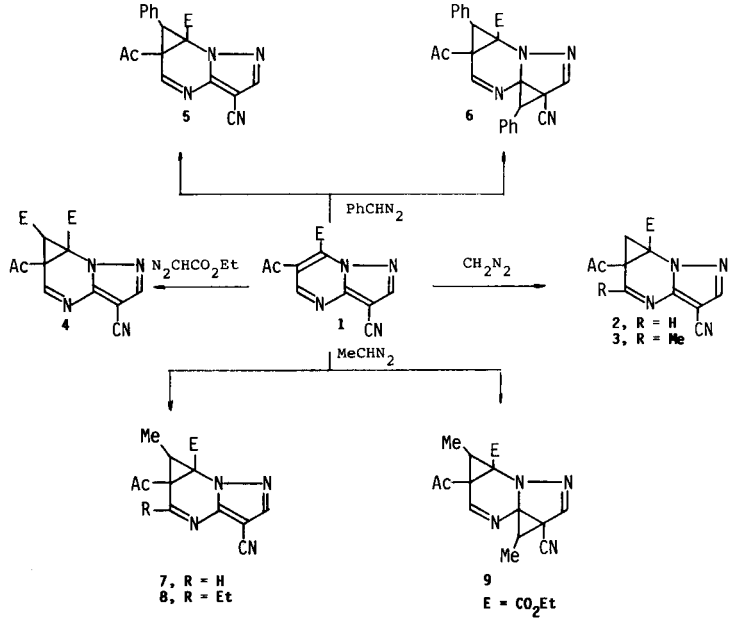
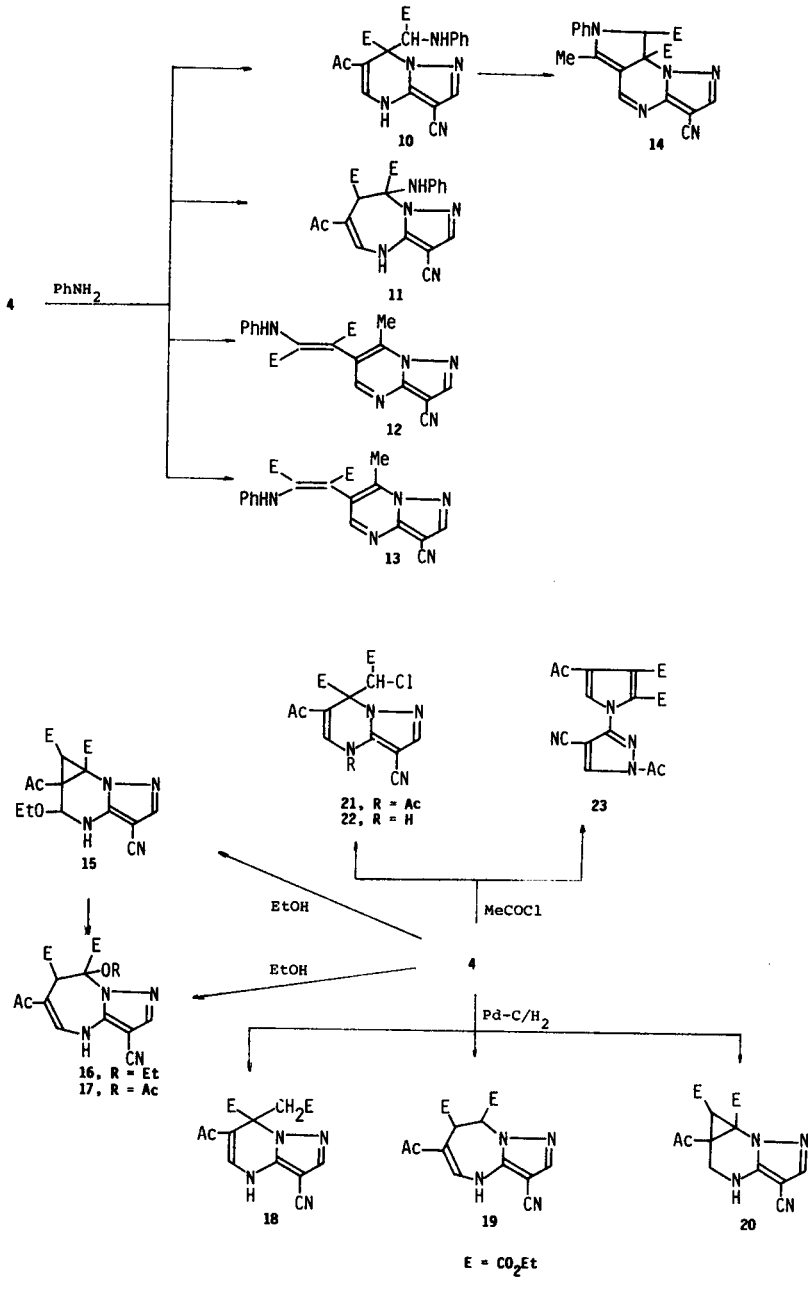


Chart 2



Reaction of **1** with diazomethane in dry ether under ice-cooling gave **7** in 31% yield, together with the recovery of the starting material in 47% yield. When treated with diazoethane at room temperature, **1** gave a complicated mixture, from which **8** (29%) and **9** (7%) were isolated by silica gel column chromatography. The sructural assignment of **9** was performed by comparison of its nmr spectrum with that of **6**.

Results and Discussion.

Previously we have reported the reaction of **2** with aniline and *N*-methylaniline [5]. Similar results were obtained by the reaction of **4** with aniline. Treatment of **4** with aniline in dry benzene at 50° afforded four products, namely **10** (42%), **11** (25%), **12** (9%), and **13** (17%). The characteristic ir, uv and nmr spectral data of these compounds are summarized in the Table.

Table

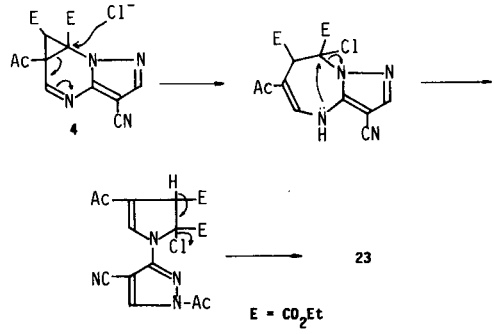
Spectral Data for Compounds **10-13**

Compound No.	IR: ν max cm^{-1}	UV: λ max nm (log ϵ)	NMR: δ
10	3200 (NH)	240 (4.33)	5.05 (1H, d, J = 9 Hz, C*H*NH)
	2220 (CN)	323 (4.16)	5.48 (1H, d, J = 9 Hz, CHN*H*)
	1750	376 (3.25)	8.00 [1H, s, C(5)-H]
	1730 (CO)		11.85 (1H, broad s, NH)
11	3300 (NH)	234 (4.33)	5.20 [1H, s, C(7)-H]
	2220 (CN)	372 (3.01)	7.85 [1H, s, C(5)-H]
	1740		6.90 (1H, broad s, NH)
	1720 (CO)		11.30 (1H, broad s, NH)
12	3400 (NH)	230 (4.32)	2.85 (3H, s, CH_3)
	2220 (CN)	363 (4.26)	8.10 [1H, s, C(2)-H]
	1720		8.53 [1H, s, C(5)-H]
	1640 (CO)		10.75 (1H, broad s, NH)
	1605 (C=C)		
13	3400 (NH)	232 (4.30)	2.80 (3H, s, CH_3)
	2220 (CN)	365 (4.25)	8.40 [each 1H, each s, C(2)-H and/or C(5)-H]
	1730		8.50 [each, 1H, each s, C(2)-H and/or C(5)-H]
	1640 (CO)		10.80 (1H, broad s, NH)
	1605 (C=C)		

The nmr spectrum of **10** revealed a pair of doublets (J = 9 Hz) at δ 5.05 and 5.48 ppm, the latter of which disappeared by the addition of deuterium oxide. This indicated the presence of -NHCH- group in this molecule. Its uv spectrum, which is characteristic to the 6-acetyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine moiety, is consistent with the structure **10**. Further, **10** cyclized to the pyrrolo[3,4-*e*]-pyrazolo[1,5-*a*]pyrimidine (**14**) by heating it in acetic acid. From the spectral data shown in the Table, it was considered that compounds **12** and **13** might be geometrical isomers with respect to the double bond. The minor product **12** isomerized readily to **13** by refluxing in benzene in the presence of *p*-toluenesulfonic acid. By comparison of their thermodynamical stabilities of **12** and **13** with those of the compounds *E*- and *Z*-β-*N*-methylanilino-3-cyano-7-methyl-6-pyrazolo[1,5-*a*]pyrimidinacrylates [2a], it was supposed that **12** is the *Z*-isomer and **13** is the *E*-isomer. The reaction sequence of **4** with aniline is thought to proceed in the same manner as that of **2** with *N*-methylaniline.

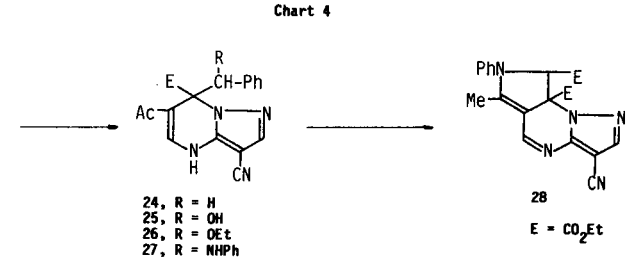
Refluxing of **4** in ethanol for 10 hours afforded **15** which was then transformed into 6-acetyl-7,8-diethoxycarbonyl-7,8-dihydro-8-ethoxy-4*H*-pyrazolo[1,5-*a*][1,3]diazepine-3-carbonitrile (**16**) on refluxing in ethanol for additional 3 days. The diazepine **16** was also obtained by refluxing **4** in ethanol for 3 days. The structural assignment of **16** was performed on the basis of analytical data and by comparison of the spectral data with those of **11**. Analogously, upon refluxing in acetic acid, **4** gave 8-acetoxy-4*H*-pyrazolo[1,5-*a*][1,3]diazepine (**17**). Catalytic hydrogenation of **4** in presence of 5% palladium-carbon gave three products, **18** (33%), **19** (44%), and **20** (3%), whose results have been reported as a short communication [1]. Compound **4** was then treated with acetyl chloride and pyridine in refluxing benzene to give a mixture of **21** (16%) and **23** (24%). The acetate **21**, on treatment with silicagel in chloroform, was hydrolyzed to **22**, whose spectral data was closely similar to those of **10**. The product **23** having the molecular formula of $C_{16}H_{18}N_4O_5$ exhibited two aromatic protons at δ 7.84 and 8.55 ppm as each singlet signal in its nmr spectrum and no characteristic absorption maximum in its uv spectrum, whose data are similar to those of 1-pyrazol-3-ylpyrole [2b]. On the basis of these results, **23** was assigned to be 4-acetyl-1-(1-acetyl-4-cyanopyrazol-3-yl)-2,3-diethoxycarbonylpyrrole. A plausible mechanism for the transformation of **4** into **23** is shown in Chart 3; *i.e.*, the first stage might involve nucleophilic attack of the chloro anion at the C(6)-position of **4** to form the intermediate dihydrodiazepine. Recyclization and dehydrochlorination would result in the ultimate formation of **23**. Based on these results, it may be concluded that 4 has reactive positions at C(6) and C(6a).

Chart 3



Catalytic hydrogenation of **5** gave **24** in 84% yield as a sole product. Upon refluxing in aqueous dioxane or in ethanol, **5** afforded **25** or **26** in moderate yields, respectively. Treatment of **5** with aniline in refluxing benzene for 2 hours gave **27** in 82% yield, which cyclized to **28** by refluxing it in benzene including a small amount of acetic acid. These results clearly demonstrate that **5** has a reactive position at C(6).

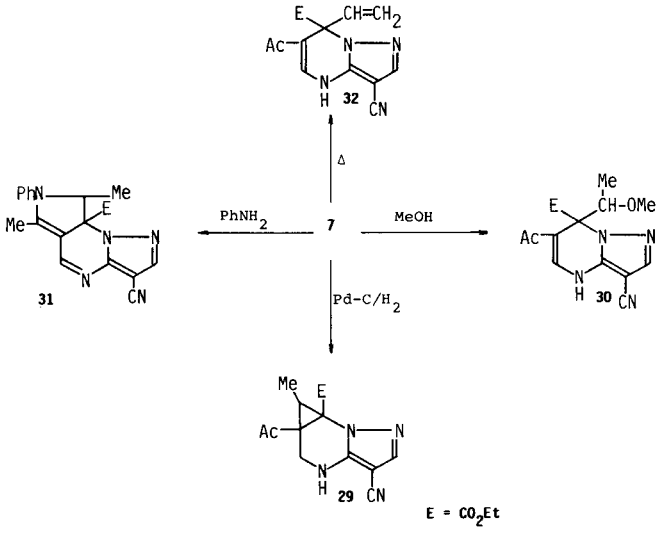
Chart 4



In contrast to the cases of **4** or **5**, catalytic hydrogenation of **7** gave the 4,5-dihydro derivative **29** in 66% yield. Refluxing **7** with methanol afforded **29** in 66% yield. Refluxing **7** with methanol afforded **30**. Treatment of **7** with aniline in refluxing benzene gave the pyrrolo[3,4-*e*]pyrazolo[1,5-*a*]pyrimidine (**31**) in 82% yield. These results were very similar to those of **5**.

Interestingly, pyrolysis of **7** in refluxing xylene gave 6-acetyl-4,7-dihydro-7-ethoxycarbonyl-7-vinylpyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (**32**) in 25% yield.

Chart 5



EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO model IRA-1 spectrophotometer and the uv spectra with a JASCO UVIDEC-505 spectrophotometer. The nmr spectra were recorded with a Hitachi R-24A spectrometer with tetramethylsilane as an internal standard. The mass spectra were recorded with a Hitachi RMU-7L spectrometer.

5a-Acetyl-6a-diethoxycarbonyl-5a,6a-dihydro-6*H*-cyclopropa[*e*]pyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (**4**).

A solution of 2.58 g (0.01 mole) of **1** and 2.28 g (0.02 mole) of ethyl diazoacetate in 50 ml of dry benzene was refluxed for 5 hours. After the solvent was evaporated *in vacuo*, the residue was recrystallized from ethanol giving 3.20 g (94%) of **4** as colorless needles, mp 137-138°. This was identical with an authentic sample reported before [3] by comparison of their ir and nmr spectra.

Reaction of **1** with Phenyldiazomethane.

To 40 ml of a petroleum ether solution of phenyldiazomethane, prepared from 13.5 g (0.05 mole) of *N*-(*N*-nitrosobenzylamino)methylbenzamide [4], was added 2.58 g (0.01 mole) of **1** in small portions with vigorous stirring under ice-cooling. The stirring was continued for 6 hours and the precipitate was collected by filtration. Recrystallization from ethanol gave 2.96 g (85%) of 5a-acetyl-5a,6a-dihydro-6a-ethoxycarbonyl-6-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**5**) as colorless needles, mp 139-140°; ir: ν max cm^{-1} 2220 (CN), 1745 and 1710 (CO); pmr (deuteriochloroform): δ 1.34 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.62 (3H, s, CH_3), 4.35 (1H, s, C(6)-H), 4.38 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 6.74-7.36 (5H, m, Ar-H), 7.83 (1H, s, C(2)-H), 8.55 (1H, s, C(5)-H).

Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.80; H, 4.68; N, 16.17.

The filtrate was condensed *in vacuo* and the tarry residue was subjected to silica gel column chromatography. Elution with a mixture of benzene-chloroform (1:1) gave 350 mg (8%) of 5a-acetyl-5,6-diphenyl-6a-ethoxycarbonyl-2a,3a,5a,6a-tetrahydro-3*H*,6*H*-dicyclopropa[*c*,*e*]pyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (**6**) as colorless needles, mp 199-201°, after recrystallization from ethanol; ir: ν max cm^{-1} 2220 (CN), 1735 and 1710 (CO); pmr (deuteriochloroform): δ 1.10 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.61 (3H, s, CH_3), 4.06 (1H, s, C(6)-H), 4.15 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 6.46 (1H, s, C(3)-H), 7.0-7.44 (11H, m, C(2)-H), 8.38 (1H, s, C(5)-H).

Anal. Calcd. for $C_{26}H_{22}N_4O_3$: C, 71.22; H, 5.06; N, 12.78. Found: C, 70.98; H, 5.18; N, 12.76.

Reaction of **1** with Diazoethane.

To 100 ml of an ether solution of diazoethane prepared from 23 g of nitrosoethylurea in 200 ml of ether, was added 2.58 g (0.01 mole) of **1** in small portions with vigorous stirring under ice-cooling. The stirring was continued for 12 hours at room temperature. After the solvent was evaporated *in vacuo*, the residue was subjected to silica gel column chromatography. The first benzene elution gave 910 mg (29%) of 5a-acetyl-5a,6a-dihydro-6a-ethoxycarbonyl-5-ethyl-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**8**) as colorless needles, mp 100-101°, after recrystallized from *n*-hexane; ir: ν max cm^{-1} 2220 (CN), 1730 and 1700 (CO); pmr (deuteriochloroform): δ 0.63 (3H, d, J = 6 Hz, $CHCH_3$), 1.27 (6H, t, J = 7 Hz, $CO_2CH_2CH_3$ and CH_2CH_3), 2.27 (3H, s, $COCH_3$), 2.65 (2H, q, J = 7 Hz, CH{CH}), 3.10 (1H, q, J = 6 Hz, $CHCH_3$), 4.25 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 7.18 (1H, s, C(2)-H), ms: m/z 314 (M^+).

Anal. Calcd. for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.83. Found: C, 61.33; H, 5.86; N, 17.86.

The second elution, with a mixture of benzene-chloroform (1:1), gave 220 mg (7%) of 5a-acetyl-3,6-dimethyl-6a-ethoxycarbonyl-2a,3a,5a,6a-tetrahydro-3*H*,6*H*-dicyclopropa[*c*,*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**9**) as colorless needles, mp 164-165°; ir: ν max cm^{-1} 2220 (CN), 1730 and 1700 (CO); pmr (deuteriochloroform): δ 1.13 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.45 and 1.70 (each 3H, each d, J = 6 Hz, 2 × $CHCH_3$), 2.20 (3H, s, $COCH_3$), 2.45 (1H, q, J = 6 Hz, $CHCH_3$), 3.90-4.40 (3H, m, $CHCH_3$ and $CO_2CH_2CH_3$), 7.73 (1H, s, C(2)-H), 8.47 (1H, s, C(5)-H); ms: m/z 314 (M^+).

Anal. Calcd. for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.83. Found: C, 61.25; H, 6.01; N, 17.99.

5a-Acetyl-6a-ethoxycarbonyl-5a,6a dihydro-6-methyl-6*H*-cyclopropa[*e*]-pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**7**).

To 50 ml of an ether solution of diazoethane, prepared from 23 g of nitrosoethylurea in 200 ml of ether, was added 2.58 g (0.01 mole) of **1** in small portions with vigorous stirring under ice cooling with a mixture of ice and salt. The stirring was continued for 2 hours and the insoluble precipitate was collected by filtration to give 1.22 g (47%) of the starting material. The filtrate was condensed *in vacuo* to provide a viscous oil which crystallized on addition of ethyl acetate. The collected precipitate was recrystallized from a mixture of ethyl acetate-*n*-hexane to give 887 mg (31%) of **7** as colorless needles, mp 132-133°; ir: ν max cm^{-1} 2220 (CN), 1740 and 1710 (CO); pmr (deuteriochloroform): δ 0.70 (3H, d, J = 6 Hz, CH_2CH_3), 4.30 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 2.50 (3H, s, $COCH_3$), 3.10 (1H, s, J = 6 Hz, $CHCH_3$), 4.30 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 7.85 (1H, s, C(2)-H), 8.47 (1H, s, C(5)-H); ms: m/z 286 (M^+).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.91; H, 4.94; N, 19.56.

Reaction of **4** with Aniline.

A mixture of 3.44 g (0.01 mole) of **4** and 1.41 g (0.015 mole) of aniline in 100 ml of dry benzene was refluxed for 1.5 hours, then cooled. The resulting precipitate was collected by filtration to give 1.84 g (42%) of ethyl 6-acetyl-3-cyano-7-ethoxycarbonyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-7-(α-anilino)acetate (**10**) as pale yellow needles, mp 255-258°; after re-

crystallization from ethanol; pmr (deuteriodimethylsulfoxide): δ 0.90-1.20 (6H, m, 2 × $CO_2CH_2CH_3$), 2.30 (3H, s, $COCH_3$), 3.80-4.17 (4H, m, 2 × $CO_2CH_2CH_3$), 5.05 (1H, d, J = 9 Hz, CHNH), 5.48 (1H, d, J = 9 Hz, NH), 6.45-7.22 (5H, m, Ar-H), 7.89 (1H, s, C(2)-H), 8.0 (1H, s, C(5)-H), 11.85 (1H, broad, s, NH); ms: m/z 437 (M^+)

Anal. Calcd. for $C_{22}H_{23}N_5O_5$: C, 60.40; H, 5.30; N, 16.01. Found: C, 60.35; H, 5.46; N, 15.73.

The filtrate was concentrated *in vacuo* to provide a viscous oil which crystallized on addition of ethanol. Fractional recrystallization of the collected precipitate from ethanol gave 377 mg (9%) of **12** and 712 mg (17%) of **13** as yellow needles, respectively.

Ethyl *Z*-β-Anilino-α-ethoxycarbonyl-3-cyano-7-methyl-6-pyrazolo[1,5-*a*]-pyrimidineacrylate (**12**).

This compound had mp 164-165°; pmr (deuteriochloroform): δ 1.15 (6H, t, J = 7 Hz, 2 × $CO_2CH_2CH_3$), 2.85 (3H, s, CH_3), 4.20 (4H, m, 2 × $CO_2CH_2CH_3$), 7.10-7.30 (5H, m, Ar-H), 8.10 (1H, s, C(2)-H), 8.53 (1H, s, C(5)-H), 10.75 (1H, broad s, NH).

Anal. Calcd. for $C_{22}H_{21}N_5O_4$: C, 63.00; H, 5.05; N, 16.70. Found: C, 63.22; H, 4.85; N, 16.81.

Ethyl *E*-β-Anilino-α-ethoxycarbonyl-3-cyano-7-methyl-6-pyrazolo[1,5-*a*]-pyrimidineacrylate (**13**).

This compound had mp 162-163°; pmr (deuteriochloroform): δ 0.75 (6H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.20 (3H, s, J = 7 Hz, $CO_2CH_2CH_3$), 2.80 (3H, s, CH_3), 3.83 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.20 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 7.10-7.40 (5H, m, Ar-H), 8.40 and 8.50 (each 1H, each s, C(2)-H and/or C(5)-H), 10.80 (1H, broad s, NH).

Anal. Calcd. for $C_{22}H_{21}N_5O_4$: C, 63.00; H, 5.05; N, 16.70. Found: C, 62.77; H, 4.85; N, 16.72.

The residual oil, which was obtained by evaporation of ethanol, was subjected to silica gel column chromatography. The first chloroform elution gave 1.09 g (25%) of 6-acetyl-8-anilino-7,8-diethoxycarbonyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepine-3-carbonitrile (**11**) as colorelss needles, mp 162-164°, after recrystallization from a mixture of benzene-ligroin; pmr (deuteriodimethylsulfoxide): δ 0.85 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.30 (3H, s, $COCH_3$), 3.95 (4H, m, 2 × $CO_2CH_2CH_3$), 5.20 (1H, s, C(7)-H), 6.90 (1H, broad s, NH), 7.85 (1H, s, C(5)-H), 11.30 (1H, broad s, NH).

Anal. Calcd. for $C_{22}H_{23}N_5O_5$: C, 60.40; H, 5.30; N, 16.01. Found: C, 60.47; H, 5.27; N, 16.13.

8a,9-Diethoxycarbonyl-8a,9-dihydro-2-methyl-1-phenyl-1*H*-pyrrolo[3,4-*e*]-pyrazolo[1,5-*a*]pyrimidine-5-carbonitrile (**14**).

A solution of 220 mg (0.5 mmole) of **10** in 10 ml of acetic acid was heated at 60° for 2 hours. After removal of the solvent by evaporation, the residue was recrystallized from ethanol to give 100 mg (48%) of **14** as yellow needles, mp 175-177°; ir: ν max cm^{-1} 2220 (CN), 1750 (CO); pmr (deuteriochloroform): δ 0.90-1.20 (6H, m, 2 × $CO_2CH_2CH_3$), 2.10 (3H, s, CH_3), 3.90-4.15 (4H, m, 2 × $CO_2CH_2CH_3$), 6.45 (1H, s, CH), 7.50 (5H, broad s, Ar-H), 8.05 (1H, s, C(6)-H), 8.35 (1H, s, C(3)-H).

Anal. Calcd. for $C_{22}H_{21}N_5O_4$: C, 63.00; H, 5.05; N, 16.70. Found: C, 63.09; H, 4.96; N, 16.61.

5a-Acetyl-6,6a-diethoxycarbonyl-5-ethoxy-4,5,5a,6a-tetrahydro-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**15**).

A solution of 344 mg (1 mmole) of **4** in 50 ml of ethanol was refluxed for 10 hours. After removal of the solvent by evaporation, the residue was recrystallized from a mixture of benzene-ligroin to give 218 mg (56%) of **15** as colorless needles, mp 182-184°; ir: ν max cm^{-1} 330 (NH), 2220 (CN), 1760 and 1730 (CO); pmr (deuteriochloroform): δ 1.0-1.30 (9H, m, 2 × $CO_2CH_2CH_3$ and OCH_2CH_3), 2.35 (3H, s, $COCH_3$), 3.23 (1H, s, C(6)-H), 3.50-4.35 (6H, m, 2 × $CO_2CH_2CH_3$ and OCH_2CH_3), 5.45 (1H, d, J = 6 Hz, CH), 7.73 (1H, s, C(2)-H), 9.18 (1H, d, J = 6 Hz, NH).

Anal. Calcd. for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.60; H, 5.53; N, 14.60.

5a-Acetyl-7,8-diethoxycarbonyl-7,8-dihydro-8-ethoxy-4*H*-pyrazolo[1,5-*a*]-[1,3]diazepine-3-carbonitrile (**16**).

A solution of 688 mg (2 mmoles) of **4** in 50 ml of ethanol was refluxed for 5 days. After removal of the solvent by evaporation, the residue was recrystallized from a mixture of ethyl acetate-*n*-hexane ro give 602 mg (77%) of **16** as colorless needles, mp 152-153°; ir: ν max cm^{-1} 3400 (NH), 2220 (CN), 1760 and 1735 (CO); uv: λ max nm (log ε) 319 (4.33), 373 (3.02); pmr (deuteriochloroform): δ 1.02-1.33 (9H, m, 2 × $CO_2CH_2CH_3$ and OCH_2CH_3), 2.39 (3H, s, $COCH_3$), 3.55-4.33 (6H, m, 2 × $CO_2CH_2CH_3$ and OCH_2CH_3), 4.90 (1H, s, C(7)-H), 7.33 (1H, d, J = 7 Hz, C(5)-H), 7.54 (1H, s, C(2)-H), 8.80 (1H, d, J = 7 Hz, NH).

Anal. Calcd. for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.24; H, 5.76; N, 14.42.

8-Acetoxy-6-acetyl-7,8-diethoxycarbonyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*]-[1,3]diazepine-3-carbonitrile (**17**).

A solution of 344 mg (1 mmole) of **4** in 20 ml of acetic acid was refluxed for 6 hours. After removal of the solvent by evaporation, a residual red oil crystallized on addition of ethanol. The collected precipitate was recrystallized from ethanol to give 120 mg (30%) of **17** as colorless needles, mp 242-245°; ir: ν max cm^{-1} 3400 (NH), 2220 CN), 1740 (CO); uv: λ max nm (log ε) 320 (4.35), 375 (2.98); pmr (deuteriodimethylsulfoxide): δ 0.97-1.35 (6H, m, 2 × $CO_2CH_2CH_3$), 1.98 and 2.28 (each 3H, each s, $COCH_3$ and $OCOCH_3$), 5.50 (1H, s, C(7)-H), 7.47 (1H, s, C(5)-H), 7.95 (1H, s, C(2)-H), 11.30 (1H, s, NH).

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.86. Found: C, 53.39; H, 5.01; N, 13.71.

Catalytic Hydrogenation of **4**.

A solution of 688 mg (2 mmoles) of 4 in 70 ml of dioxane was shaken with hydrogen over 0.5 g of 5% palladium-carbon for 24 hours using a Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo*, and the residue was recrystallized from ethanol to give 304 mg (44%) of ethyl 6-acetyl-3-cyano-4,7-dihydro-7-ethoxycarbonylpyrazolo-[1,5-*a*]pyrimidine-7-carboxylate (**18**) as pale yellow needles, mp 178-179°; ir: ν max cm^{-1} 3300 (NH), 2220 (CN), 1755 and 1720 (CO); pmr (deuteriodimethylsulfoxide): δ 1.0-1.20 (6H, m, 2 × $CO_2CH_2CH_3$), 2.25 (3H, s, $COCH_3$), 3.15 and 3.42 (each 1H, each d, J = 15 Hz, CH_2), 3.85 (2H, q, J 5 7 Hz, $CO_2CH_2CH_3$), 4.05 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 7.75 and 7.90 (each 1H, each s, C(2)-H and/or C(5)-H), 11.50 (1H, broad s, NH); uv: λ max (log ε) 253 (4.25), 315 (4.15), and 386 (3.75).

Anal. Calcd. for $C_{16}H_{18}N_4O_5$: C, 55.48; H, 5.24; N, 16.18. Found: C, 55.34; H, 5.28; N, 16.25.

The filtrate was concentrated *in vacuo*, and the residue was recrystallized from a mixture of ethanol and *n*-hexane to give 227 mg (33%) of 6-acetyl-7,8-diethoxycarbonyl-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,3]diazepine-3-carbonitrile (**19**) as colorless needles, mp 178-179°; ir: ν max cm^{-1} 3300 (NH), 2220 (CN), 1755 and 1730 (CO); uv: λ max nm (log ε), 323 (4.33), 370 (2.88); pmr (deuteriochloroform): δ 1.0-1.10 (6H, m, 2 × $CO_2CH_2CH_3$), 2.27 (3H, s, $COCH_3$), 3.80-4.15 (4H, m, 2 × $CO_2CH_2CH_3$), 4.78 (1H, d, J = 5 Hz, C(8)-H), 5.95 (1H, d, J = 5 Hz, C(7)-H), 7.33 (1H, s, C(5)-H), 7.83 (1H, s, C(2)-H), 10.74 (1H, broad s, NH).

Anal. Calcd. for $C_{16}H_{18}N_4O_5$: C, 55.48; H, 5.24; N, 16.18. Found: C, 55.21; H, 5.22; N, 16.24.

The filtrate was concentrated *in vacuo*, and the residue was subjected to silica gel column chromatography. Elution with chloroform gave **21** mg (3%) of 5a-acetyl-6,6a-diethoxycarbonyl-4,5,5a,6a-tetrahydro-6*H*-cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**20**) as colorless needles, mp 170-172°; ir: ν max cm^{-1} 3200 (NH), 2220 (CN), 1730 (CO); pmr (deuteriodimethylsulfoxide): δ 1.13 (6H, t, J = 7 Hz, 2 × $CO_2CH_2CH_3$), 2.33 (3H, s, $COCH_3$), 3.30 (1H, s, C(6)-H), 3.58 and 3.73 (each 1H, each broad s, CH_3), 3.85-4.25 (4H, m, 2 × $CO_2CH_2CH_3$), 7.62 (1H, s, C(2)-H), 7.90 (1H, broad s, NH).

Anal. Calcd. for $C_{16}H_{18}N_4O_5$: C, 55.48; H, 5.24; N, 16.18. Found: C, 55.43; H, 5.33; N, 15.92.

Reaction of **4** with Acetyl Chloride.

Five drops of pyridine were added to a solution of 688 mg (2 mmoles) of 4 and 1.6 ml of acetyl chloride in 30 ml of benzene and the mixture was refluxed for 3 days, then cooled. The mixture was washed with water,

saturated sodium bicarbonate solution and dried over sodium sulfate. After removal of the solvent by evaporation, the residue was subjected to silica gel column chromatography. The first fraction eluted with a mixture of benzene-chloroform (1:1) gave 180 mg (23%) of 4-acetyl-1-(1-acetyl-4-cyanopyrazol-3-yl)-2,3-diethoxycarbonylpyrole (**23**) as colorless needles, mp 145-146°, after recrystallization from a mixture of ethyl acetate-*n*-hexane; ir: ν max cm^{-1} 2220 (CN), 1745, 1730 and 1685 (CO); pmr (deuteriodimethylsulfoxide): δ 1.18 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.32 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.44 and 2.48 (each 3H, each s, $COCH_3$ and/or NCH_3), 4.17 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.36 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 7.84 (1H, s, pyrrole ring-H), 8.55 (1H, s, pyrazole ring-H).

Anal. Calcd. for $C_{18}H_{18}N_4O_6$: C, 55.95; H, 4.70; N, 14.50. Found: C, 55.85; H, 4.49; N, 14.50.

The second fraction eluted with chloroform gave 126 mg (16%) of ethyl 3-cyano-4,6-diacetyl-4,7-dihydro-7-ethoxycarbonylpyrazolo[1,5-*a*]-pyrimidine-7-(α-chloro)acetate (**21**) as colorless needles, mp 142-143°, after recrystallization from a mixture of ethanol-*n*-hexane; ir: ν max cm^{-1} 2220 (CN), 1740 (CO); pmr (deuteriodimethylsulfoxide): δ 1.19 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.28 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.53 (3H, s, $COCH_3$), 2.78 (3H, s, $NCOCH_3$), 4.20 (4H, m, 2 × $CO_2CH_2CH_3$), 5.25 (1H, s, CH), 8.07 and 8.38 (each 1H, each s, C(2)-H and/or C(5)-H).

Anal. Calcd. for $C_{18}H_{19}ClN_4O_6$: C, 51.13; H, 4.53; N, 13.25. Found: C, 50.98; H, 4.57; N, 13.52.

Ethyl 6-Acetyl-3-cyano-4,7-dihydro-7-ethoxycarbonylpyrazolo[1,5-*a*]pyrimidine-7-(α-chloro)acetate (**22**).

A suspended mixture of 212 mg (0.5 mmole) of **21** and 5 g of silica gel in 50 ml of chloroform was vigorously stirred for 2 days. The reaction mixture was filtered and the filtrate was condensed *in vacuo*. The residue was recrystallized from ethanol to give 124 mg (65%) of **22**, mp 191-193°; ir: ν max cm^{-1} 3200 (NH), 2220 (CN), 1750 and 1730 (CO); uv: λ max nm (log ϵ) 242 (4.33), 325 (4.15), 376 (3.23); pmr (deuteriodimethylsulfoxide): δ 1.14 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.21 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.31 (3H, s, $COCH_3$), 3.90-4.30 (4H, m, 2 × $CO_2CH_2CH_3$), 5.23 (1H, s, CH), 8.03 and 8.05 (each 1H, each s, C(2)-H and/or C(5)-H), 11.90 (1H, broad s, NH).

Anal. Calcd. for $C_{16}H_{17}ClN_4O_5$: C, 50.46; H, 4.50; N, 14.71. Found: C, 50.25; H, 4.63; N, 14.59.

6-Acetyl-7-benzyl-4,7-dihydro-7-ethoxycarbonylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**24**).

A solution of 348 mg (1 mmole) of **5** in 50 ml of dioxane was shaken with 0.2 g of 5% palladium-carbon for 3 hours using a Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo* to give a viscous oil which crystallized on addition of ethanol. Recrystallization from ethanol gave 292 mg (84%) of **24** as pale yellow needles, mp 215-216°; ir: max cm^{-1} 3200 (NH), 2220 (CN), 1740 and 1700 (CO); uv: λ max nm (log ϵ) 255 (4.27), 316 (4.13), 387 (3.66); pmr (deuteriochloroform): δ 1.24 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.31 (3H, s, $COCH_3$), 3.63 (2H, q, J = 26 Hz, CH_2), 4.22 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 6.36-7.20 (5H, m, Ar-H), 7.28 (1H, s, C(2)-H), 7.64 (1H, s, C(5)-H), 8.50 (1H, broad s, NH).

Anal. Calcd. for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 64.87; H, 5.41; N, 16.17.

6-Acetyl-4,7-dihydro-7-ethoxycarbonyl-7-(α-hydroxy)benzylpyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (**25**).

A solution of 696 mg (2 mmoles) of **5** in 50 ml of 70% aqueous dioxane was refluxed for 2 days. After removal of the solvent by evaporation, the residue was recrystallized from a mixture of ethyl acetate-*n*-hexane to give 540 mg (74%) of **25** as colorless needles, mp 180-181°; ir: ν max cm^{-1} 300-3200 (NH and OH), 2220 (CN), 1730 and 1700 (CO); uv: λ max nm (log ϵ) 255 (4.30), 318 (4.20), 385 (3.55); pmr (deuteriodimethylsulfoxide): δ 1.20 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.23 (3H, s, $COCH_3$), 4.22 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.95 (1H, d, J = 3 Hz, OH), 5.38 (1H, d, J = 3 Hz, CH), 6.60-7.18 (5H, m, Ar-H), 7.38 (1H, s, C(2)-H), 7.64 (1H, s, C(5)-H).

6-Acetyl-4,7-dihydro-7-(α-ethoxybenzyl)-7-ethoxycarbonylpyrazolo[1,5-*a*]-pyrimidine-3-carbonitrile (**26**).

A mixture of 696 mg (2 mmoles) of **5** in 50 ml of ethanol was refluxed for 5 days. After removal of the solvent by evaporation, the residue was recrystallized from ethyl acetate to give 560 mg (71%) of **26** as colorless needles, mp 238-239°; ir: ν max cm^{-1} 3300 (NH), 2220 (CN), 1740 and 1705 (CO); uv: λ max nm (log ϵ) 257 (4.28), 320 (4.18), 383 (3.81); pmr (deuteriochloroform): δ 0.88 (3H, t, J = 7 Hz, OCH_2CH_3), 1.19 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.17 (3H, s, $COCH_3$), 2.90-3.37 (2H, m, OCH_2CH_3), 4.20 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 5.24 (1H, s, CH), 7.07-7.40 (5H, m, Ar-H), 7.47 (1H, d, J = 6 Hz, C(5)-H), 7.67 (1H, s, C(2)-H), 9.08 (1H, broad d, J = 6 Hz, NH).

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.21. Found: C, 63.91; H, 5.81; N, 14.16.

6-Acetyl-4,7-dihydro-7-ethoxycarbonyl-7-(α-anilino)benzylpyrazolo[1,5-*a*]-pyrimidine-3-carbonitrile (**27**).

A solution of 348 mg (1 mmole) of **5** and 113 mg (1.2 mmoles) of aniline in 50 ml of dry benzene was heated t 50° for 2 hours. After removal of the solvent by evaporation, the residue was recrystallized from ethanol to give 358 mg (82%) of **27** as pale yellow needles, mp 228-229°; ir: ν max cm^{-1} 3400 and 3200 (NH), 2220 (CN), 1740 and 1700 (CO); uv: λ max nm (log ϵ) 252 (4.33), 324 (4.20), 384 (3.48); pmr (deuteriodimethylsulfoxide): δ 1.0 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.25 (3H, s, $COCH_3$), 4.08 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 5.17 (1H, d, J = 6 Hz, CH), 6.18 (1H, d, J = 6 Hz, NH), 6.38-7.30 (10H, m, Ar-H), 7.45 (1H, s, C(5)-H), 8.22 (1H, s, C(2)-H), 11.0 (1H, broad s, NH).

Anal. Calcd. for $C_{25}H_{23}N_5O_3$: C, 68.01; H, 5.25; N, 15.87. Found: C, 67.85; H, 5.25; N, 15.78.

8a,9-Dihydro-1,9-diphenyl-8a-ethoxycarbonyl-2-methyl-1*H*-pyrazolo[3,4-*e*]-pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**28**).

A solution of 441 mg (1 mmole) of **27** in 50 ml of benzene and 1 ml of acetic acid was refluxed for 10 hours. After removal of the solvent by evaporation, the residue was recrystallized from a mixture of benzene-*n*-hexane to give 372 mg (88%) of **28** as yellow needles, mp 197-198°; ir: ν max cm^{-1} 2220 (CN), 1730 (CO); pmr (deuteriodimethylsulfoxide): δ 0.81 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.28 (3H, s, CH_3), 3.66 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 6.91 (1H, s, C(8)-H), 8.07 (1H, s, C(2)-H), 8.40 (1H, s, C(5)-H).

Anal. Calcd. for $C_{25}H_{21}N_5O_5$: C, 70.90; H, 5.00; N, 16.54. Found: C, 70.78; H, 4.81; N, 16.37.

5a-Acetyl-6a-ethoxycarbonyl-6-methyl-4,5,5a,6a-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (**29**).

A solution of 286 mg (1 mmole) of **7** in 50 ml of dioxane was shaken with hydrogen over 150 mg of 5% palladium-carbon using a Skita apparatus for 12 hours. The reaction mixture was filtered and concentrated *in vacuo*. The residue was recrystallizaed from benzene to give 196 mg (66%) of **29** as colorless needles, mp 168-169°; ir: ν max cm^{-1} 3300 (NH), 2220 (CN), 1735 and 1710 (CO); pmr (deuteriochloroform): δ 1.02 (3H, d, J = 6 Hz, $CHCH_3$), 1.22 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.32 (3H, s, $COCH_3$), 2.87 (1H, q, J = 6 Hz, C(6)-H), 3.36 and 3.97 (2H, q, J = 13 Hz, CH_2), 4.17 (2H, q, J = 7 Hz, $CO_2CH_2H_3$), 5.68 (1H, broad s, NH), 7.52 (1H, s, C(2)-H).

Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.44. Found: C, 58.34; H, 5.73; N, 19.45.

6-Acetyl-4,7-dihydro-7-ethoxycarbonyl-7-(α-methoxy)ethylpyrazolo[1,5-*a*]-pyrimidine-3-carbonitrile (**30**).

A solution of 286 mg (1 mmole) of **7** in 50 ml of methanol was refluxed for 10 hours. After removal of the solvent by evaporation, the residue was recrystallized from a mixture of ethyl acetate-*n*-hexane to give 228 mg (72%) of **30** as colorless needles, mp 212-213°; ir: ν max cm^{-1} 3200 (NH), 2220 (CN), 1730 (CO); uv: λ max nm (log ϵ) 250 (4.28), 346 (4.18), 382 (3.50); pmr (deuteriochloroform): δ 1.18 (3H, d, J = 6 Hz, $CHCH_3$), 4.26 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 7.65 (1H, broad s, C(5)-H), 7.69 (1H, s, C(2)-H), 9.33 (1H, broad s, NH).

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.78; H, 5.94; N, 17.58.

8a,9-Dihydro-3,9-dimethyl-8a-ethoxycarbonyl-1-phenyl-1*H*-pyrrolo[3,4-*e*]-pyrazolo[1,5-*a*]pyrimidine-5-carbonitrile (**31**).

A solution of 386 mg (1 mmole) of **7** and 113 mg (1.2 mmoles) of aniline in 50 ml of dry benzene was refluxed for 3 hours. After removal of the solvent by evaporation, the residue was recrystallized from ethyl acetate to give 299 mg (83%) of **31** as yellow needles, mp 166-167°; ir: ν max cm^{-1} 2220 (CN), 1730 (CO); pmr (deuteriodimethylsulfoxide): δ 1.20 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.40 (3H, d, J = 6 Hz, $CHCH_3$), 2.14 (3H, s, CH_3), 4.14 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 5.51 (1H, q, J = 6 Hz, CH), 7.30-7.53 (5H, m, Ar-H), 7.99 (1H, s, C(3)-H), 8.28 (1H, s, C(6)-H).

Anal. Calcd. for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.74; H, 5.41; N, 19.40.

6-Acetyl-4,7-dihydro-7-ethoxycarbonyl-7-vinylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**32**).

A solution of 286 mg (1 mmole) of **7** in 50 ml of dry xylene was refluxed for 5 hours, then cooled. The resulting precipitate was collected by filtration and recrystallized from a mixture of ethyl acetate-*n*-hexane to give 72 mg (25%) of **32** as pale yellow needles, mp 187-188°; ir: ν max cm^{-1} 3300 (NH), 2220 (CN), 1735 and 1710 (CO); uv: λ max nm (log ϵ) 250 (sh), 327 (4.25), 385 (3.70); pmr (deuteriochloroform): δ 1.27 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.40 (3H, s, $COCH_3$), 4.30 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.70 and 5.25 (each 1H, each d, J = 18 and 10 Hz, $=CH_2$), 6.75 (1H, dd, J = 18 and 10 Hz, -CH=), 7.60 (1H, d, J = 6 Hz, C(5)-H), 7.70 (1H, s, C(2)-H), 9.40 (1H, d, J = 6 Hz, NH).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.57; H, 4.95; N, 19.54.

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