Chem. Pharm. Bull.
30(8)2723—2731(1982)

# Reactions of Pyrazolo[1,5-*a*]pyrimidine Derivatives with Nucleophiles. III.[1] Nucleophilic Addition to 6,7-Bis(ethoxycarbonyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile in the Presence of Triethyloxonium Fluoroborate[2]

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(Received January 25, 1982)

Nucleophilic additions of phenol and aniline analogs to 6,7-bis(ethoxycarbonyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**1**) in the presence of triethyloxonium fluoroborate are described. For example, though phenol or *o*-cresol (having no substituent at the *para*-position) reacted with **1** to give the cyclohexadienylidene derivatives (**3**, **4**), *p*- or *m*-cresols, *p*-methoxyphenol, and α- or β-naphthol gave the corresponding spiro lactones (**6**, **7**, **8**, **10** and **12**). When **1** was treated with several kinds of aniline analogs, three types of products were obtained. Namely, while aniline or *o*-toluidine gave the 7-(4-aminophenyl) adducts (**13**, **15**), *p*-anisidine, *p*-chloroaniline or *p*-nitroaniline afforded the 7-anilino derivatives (**17**, **20** or **21**). Treatment of *p*-toluidine with **1** under the same reaction conditions gave a mixture of the spiro-indole-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin--2-one (**22**) and the pyrazolo[1′,5′: 1,2]pyrimido[5,6-*c*]quinoline (**23**).

**Keywords**——pyrazolo[1,5-*a*]pyrimidine; triethyloxonium fluoroborate; toluidine; naphthol; spiro{benzo[*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidine}; spiro{naphtho[1,2-*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidine}; spiro{naphtho[2,1-*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidine}; spiro{indole-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidine}; pyrazolo[1′,5′: 1,2]pyrimido[5,6-*c*]quinoline

Previously, we reported[3] the nucleophilic additions of phenol analogs, indoles, and enamines of cyclohexanone to 6,7-bis(ethoxycarbonyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**1**) in the presence of boron trifluoride ($BF_3$)-etherate. For example, when a mixture of **1** and three equivalents of phenol or a phenol analog such as *p*-cresol or β-naphthol was refluxed with a limited amount of $BF_3$-etherate in dichloromethane, diethyl 2-(4-oxo-2,5-cyclohexadienylidene)-3-[4-cyano-5(1*H*)-pyrazolylamino]methylenesuccinate, 3′-cyano-6′-ethoxycarbonyl-5-methylspiro{benzo[*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one or 3′-cyano-6′-ethoxycarbonylspiro{naphtho[2,1-*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one, respectively, was obtained. Although it was found[2] that aluminum chloride ($AlCl_3$) promotes these reactions under mild conditions to give the addition products in better yields, these catalysts were not useful for the reaction of **1** with aniline analogs, because of the formation of $BF_3$ or $AlCl_3$ complexes of anilines.

In the proceding paper,[1] we reported a synthesis and X-ray crystal structure determination of novel 1,4-dihydrocyclopent[*b*]indole derivatives, which were prepared by reaction of **1** with indoles in the presence of triethyloxonium fluoroborate ($Et_3OBF_4$). In the present paper, we wish to report the reaction of **1** with phenol analogs as well as aniline analogs in the presence of $Et_3OBF_4$, which is known to convert pyrimidines to their diquaternary salts.[4]

## Reactions with Phenol Analogs

First, nucleophilic addition of **1** with phenol itself was investigated. When a mixture of **1** with three equivalents of $Et_3OBF_4$ in dichloromethane was allowed to stand at room temperature, **1** could no longer be detected on thin layer chromatographic analysis after *ca.* 24 h. The reaction mixture was then treated with cold water to give 6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**2**) in 55.0% yield.[3] Thus, three equivalents of phenol was added to a mixture of **1** and $Et_3OBF_4$ prior to water treatment, and the whole mixture was allowed to react with stirring at room temper-

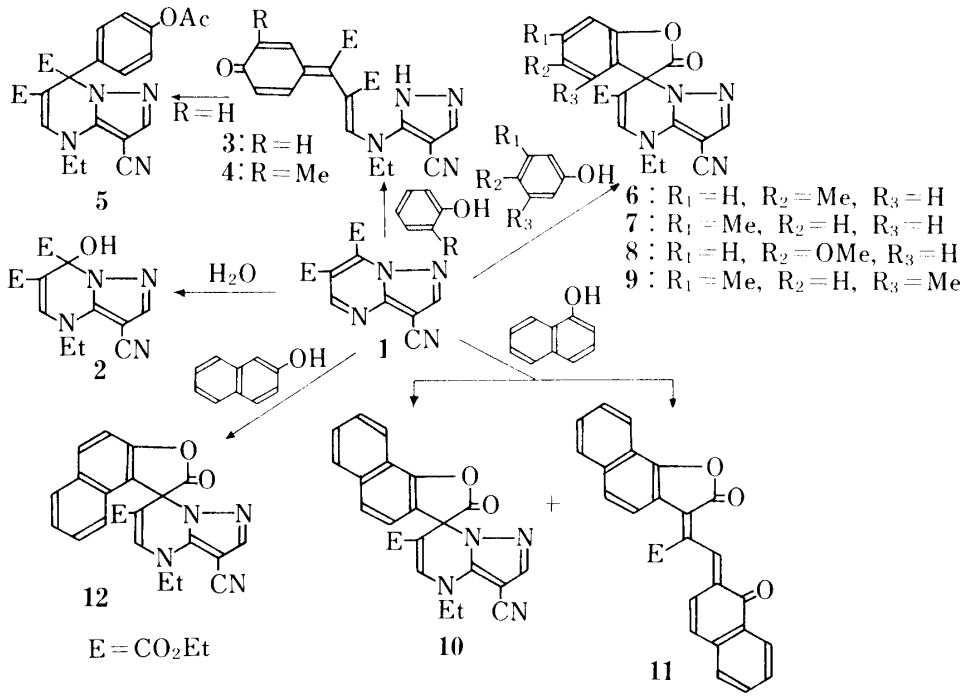



Chart 1

Table I. Analytical and IR Spectral Data for Spiro Lactones

| Compd. No. | mp (°C) | Yield (%) | Formula | Analyses (%) Calcd (Found) C | H | N | IR $\nu_{max}^{KBr}$ cm$^{-1}$ (CN) | (CO) |
|---|---|---|---|---|---|---|---|---|
| **6** | 212—214[a] | 32.7 | $C_{20}H_{18}N_4O_4$ | 63.48 (63.35) | 4.80 (4.76) | 14.81 (14.81) | 2220 | 1820 1710 |
| **7** | 196[a] | 6.6 | $C_{20}H_{18}N_4O_4$ | 63.48 (63.68) | 4.80 (4.95) | 14.81 (14.90) | 2220 | 1820 1710 |
| **8** | 184—186[a] | 15.2 | $C_{20}H_{20}N_4O_5$ | 60.91 (60.82) | 4.60 (4.36) | 14.21 (14.47) | 2220 | 1820 1690 |
| **9** | 183—184[a] | 62.8 | $C_{21}H_{20}N_4O_4$ | 64.27 (64.07) | 5.14 (5.06) | 14.28 (14.24) | 2220 | 1820 1710 |
| **10** | 245—246[b] | 59.3 | $C_{23}H_{18}N_4O_4$ | 66.66 (66.74) | 4.38 (4.16) | 13.52 (13.59) | 2220 | 1820 1710 |
| **12** | 275—277[b] | 61.8 | $C_{23}H_{18}N_4O_4$ | 66.66 (66.55) | 4.38 (4.52) | 13.52 (13.38) | 2220 | 1820 1710 |

*a*) Recrystallized from EtOH.
*b*) Recrystallized from $CH_3CN$.

ature for 24 h to give diethyl 2-(4-oxo-2,5-cyclohexadienylidene)-3-(4-cyano-5(1*H*)-pyrazolylethylamino)methylenesuccinate (**3**)[5] in 59.0% yield. On treatment with acetic anhydride in the presence of a catalytic amount of sulfuric acid, **3** was transformed into 7-(*p*-acetoxyphenyl)-6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**5**), which proved **3** to have the cyclohexadienylidene structure.[3] Therefore, subsequent reactions with other nucleophiles in this work were carried out after the completion of the reaction of **1** with $Et_3OBF_4$. Similarly, reaction of **1** with *o*-cresol afforded **4** in 43.0% yield. However, when treated with *p*- and *m*-cresols, *p*-methoxyphenol or 3,5-xylenol, **1** afforded the corresponding 4′-ethylspiro{benzo[*b*]furan-3(2*H*), 7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-ones (**6**, **7**, **8** and **9**). The analytical and infrared (IR) spectral data are summarized in Table I. Under the same experimental conditions as above, α-naphthol was treated with **1** to give a

corresponding spiro lactone (**10**) (Table I) in 59.3% yield together with ethyl α-(1,2-dihydro-1-oxo-2-naphthylidenemethyl)-2-oxo-$\Delta^{3(2H),\alpha}$-naphtho[1,2-*b*]furaneacetate (**11**), $C_{27}H_{18}O_5$, mp 231—232 °C, in 2.6% yield. Evidence for this structure was provided by the IR spectrum (in which three strong absorption bands at 1810, 1710 and 1660 $cm^{-1}$ due to carbonyl groups appeared) and the proton magnetic resonance (PMR) spectrum [in which a pair of doublets ($J$=9 Hz) at 6.75 and 7.30 ppm due to –CH=CH– (data consistent with the data for *o*-naphthoquinone)[6] as well as a singlet at 8.48 ppm due to =CH appeared].

The formation of the lactone (**11**) can be rationalized as shown in Chart 2; namely, nucleophilic attack of the second α-naphthol at the C(5′)-position of the initially formed spiro lactone (**10**) may form the intermediate A. Subsequenctly, elimination of the aminopyrazole moiety (taking the *o*-naphthoquinone structure) would ultimately yield **11**. Under the same conditions, β-naphthol reacted with **1** to give only a spiro lactone (**12**) in 61.8% yield.

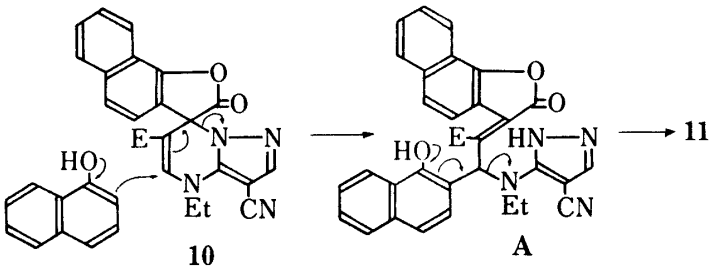



Chart 2

**Reaction with Aniline Analogs**

When **1** was treated with several kinds of aniline analogs under the same experimental conditions as above, three types of products were obtained. Namely, aniline, *N*,*N*-dimethylaniline or *o*-toluidine gave the 7-aminophenyl adducts (**13**,[7] **14** and **15**) upon reaction with

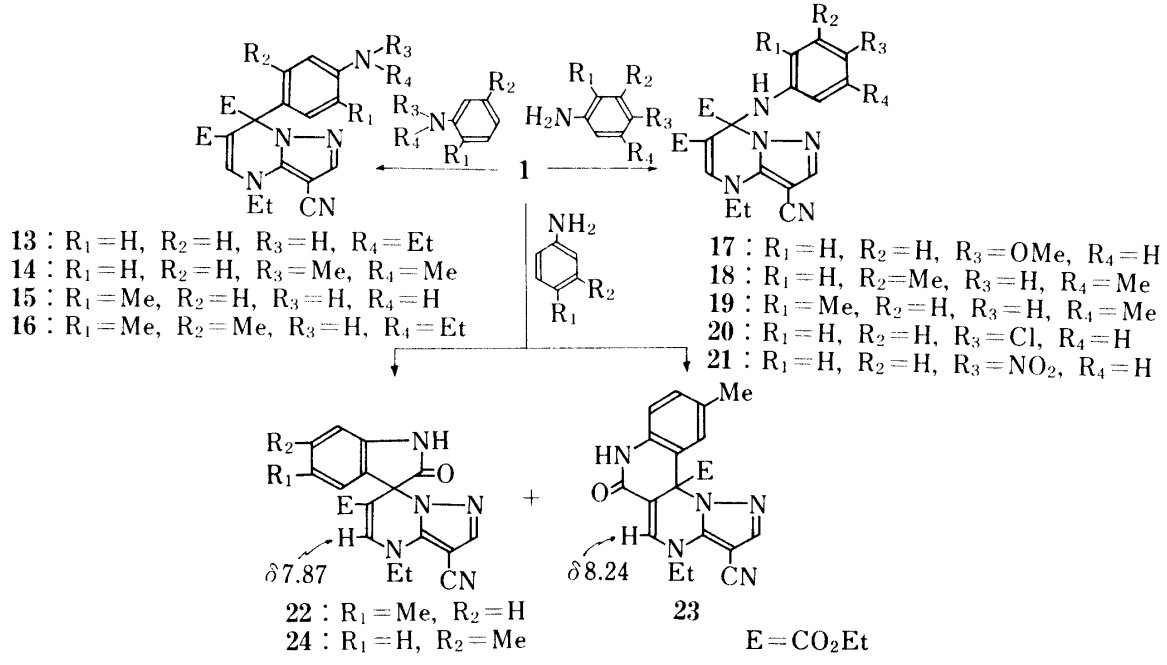
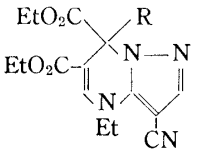


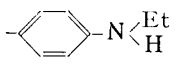
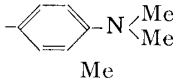
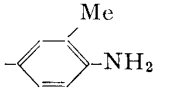
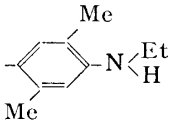
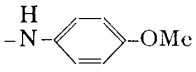
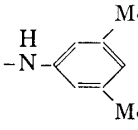
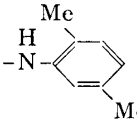
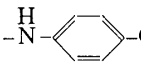
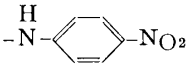

Chart 3

**1** in yields of 57.2, 19.5 and 32.8%, respectively. On the other hand, the 7-anilino derivatives (**17**, **18**, **20** and **21**) were obtained by reaction of **1** with *p*-anisidine, 3,5-xylidine, *p*-chloroaniline and *p*-nitroaniline in yields of 72.3, 47.2, 65.1 and 61.3%, respectively. In the case of 2,5-xylidine, a mixture of the 7-(4-aminophenyl) adduct (**16**)[7] and the 7-anilino derivative (**19**) was obtained (14.6 and 7.1% yields, respectively). However, we could not find a clear substituent effect on these reactions. The analytical and IR spectral data for these products (**13**—**21**) are summarized in Table II.

Finally, treatment of *p*-toluidine with **1** under the same reaction conditions as above gave a 19.9% yield of 3′-cyano-6′-ethoxycarbonyl-4′-ethyl-5-methylspiro{indole-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one (**22**) together with an 8.0% yield of 3-cyano-11*b*-ethoxycarcarbonyl-4-ethyl-10-methyl-4,6,7,11*b*-tetrahydropyrazolo[1′,5′: 1,2]pyrimido[5,6-*c*]quinolin-

Table II. Analytical and IR Spectral Data for 7-Substituted 4,7-Diydropyrazolo [1,5-*a*]pyrimidines Compd.



| Compd. No. | R | mp (°C) | Formula | Analyses (%) Calcd (Found) C | H | N | IR $\nu_{max}^{KBr}$ cm$^{-1}$ (NH) | (CN) | (CO) |
|---|---|---|---|---|---|---|---|---|---|
| **13** |  | 124—127[a] | $C_{23}H_{27}N_5O_4$ | 63.14 (62.85) | 6.22 (6.38) | 16.01 (15.97) | 3400 | 2220 | 1760 1690 |
| **14** |  | 105—106[b] | $C_{23}H_{27}N_5O_4$ | 63.14 (62.95) | 6.22 (6.22) | 16.01 (15.88) | | 2220 | 1760 1690 |
| **15** |  | 161—162[a] | $C_{22}H_{25}N_5O_4$ | 62.40 (62.68) | 5.95 (6.19) | 16.54 (16.40) | 3440 3380 | 2220 | 1740 1690 |
| **16** |  | 155—156[c] | $C_{25}H_{31}N_5O_4$ | 64.49 (64.16) | 6.71 (6.64) | 15.04 (15.22) | 3400 | 2220 | 1740 1690 |
| **17** |  | 139[a] | $C_{22}H_{25}N_5O_5$ | 60.12 (59.94) | 5.73 (5.52) | 15.94 (15.72) | 3320 | 2220 | 1760 1700 |
| **18** |  | 147[a] | $C_{23}H_{27}N_5O_4$ | 63.14 (62.98) | 6.22 (5.95) | 16.01 (16.24) | 3400 | 2220 | 1760 1700 |
| **19** |  | 129—130[b] | $C_{23}H_{27}N_5O_4 \cdot 1/2\,C_6H_6$ | 65.53 (65.72) | 6.35 (6.53) | 14.70 (14.97) | 3480 | 2220 | 1760 1710 |
| **20** |  | 170—171[e] | $C_{21}H_{22}ClN_5O_4 \cdot {}^1/_2C_6H_6$ | 56.82 (57.02) | 5.00 (5.13) | 15.78 (15.61) | 3320 | 2220 | 1760 1690 |
| **21** |  | 204—205[e] | $C_{21}H_{22}N_6O_6$ | 55.50 (55.53) | 4.88 (4.88) | 18.50 (18.22) | 3330 | 2220 | 1760 1690 |

*a*) Recrystallized from EtOH.
*b*) Recrystallized from $CH_3CN$.
*c*) Recrystallized from AcOEt–*n*-hexane.
*d*) Recrystallized from benzene–ligroin.
*e*) Recrystallized from MeOH.

6-one (**23**). As depicted in Chart 3, the PMR spectrum, in which the signal due to the C(5)-proton of **23** appeared down-field (by 0.37 ppm) from that of **22**, strongly supports the structure of **23** as a $\delta$-lactam, because the C(5)-proton of **23** is located in the deshielding zone of the $\delta$-lactam carbonyl group from an inspection of a Dreiding model. Moreover, evidence for the spiro lactam structure of **22** was provided by its ultraviolet (UV) spectrum [$\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 324 (3.08)], in which the absorption maximum is very similar to that of the corresponding spiro lactone (**6**). Similarly, *m*-toluidine gave only the spiro lactam (**24**) in 39.4% yield.

**Reactions with Miscellaneous Nucleophiles**

When 8-hydroxyquinoline was allowed to react with **1** under the same experimental conditions, 6,7-bis (ethoxycarboxyl)-4,7-dihydro-4-ethyl-7-(8-hydroxy-5-quinolyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**25**), which gave a positive ferric cholride test, was isolated in 18.4% yield as an unexpected product. In contrast to the reaction with indoles described in the preceding paper,[1] **1** reacted with benzo[*b*]furan to give 7-(2-benzo[*b*] furanyl)-6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethylpyrazolo[1,5-*a*] pyrimidine-3-carbonitrile (**26**) in 47.4% yield, and the PMR spectrum of this product showed a singlet at 7.10 ppm due to the $\beta$-proton of benzofuran.[8] Finally, as described in the experimental section, potassium carbonate remarkably promoted the reaction of **1** with acetone to give 7-acetonyl-6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**27**) in 43.1% yield. The structural assignment of **27** was based on the analytical and spectral data detailed in the experimental section.

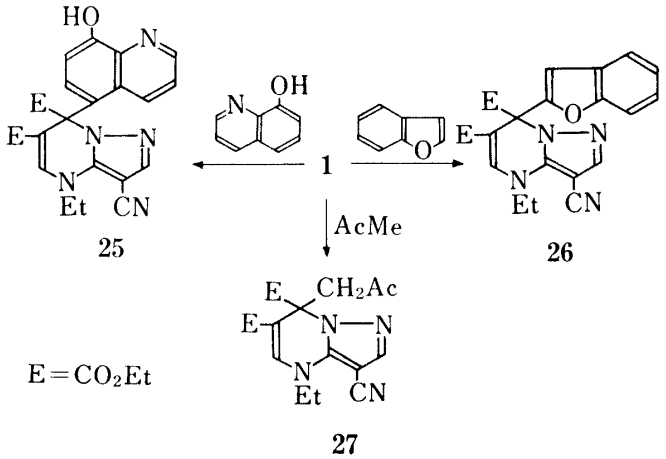



Chart 4

On the basis of these investigations, it can be concluded that triethyloxonium fluoroborate is a more effective catalyst than $BF_3$-etherate for the reaction of **1** with nucleophiles.

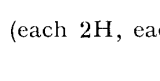
## Experimental

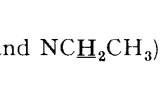
All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were recorded on a JASCO model IRA-1 spectrophotometer and the UV spectra on a JASCO UVIDEC-505 spectrophotometer. The PMR spectra were taken at 90 MHz with a Hitachi R-24A spectrometer and chemical shifts are expressed in ppm downfield from TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. The MS were recorded with a Hitachi RMU-7L spectrometer.

**6,7-Bis(ethoxycarbonyl)-4,7-dihydro-4-ethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (2)**——Three mmol of $Et_3OBF_4$ was added to a solution of 1 mmol of **1** in 5 ml of $CH_2Cl_2$, and the mixture was allowed to stand at room temperature for 24 h. The $CH_2Cl_2$ solution was washed with cold water (10 ml×5), dried over $Na_2SO_4$ and concentrated. The residue was recrystallized from benzene–ligroin mixture to give 184 mg (55.0%) of **2** as colorless needles of mp 130—131°C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3440 (OH), 2220 (CN), 1750, 1700 (CO). PMR ($CDCl_3$) $\delta$: 1.20—1.76 (9H, m, 2×$CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 4.00—4.50 (6H, m, 2×$CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 5.74 (1H, s, OH), 7.60 and 7.77 [each 1H, each s, C(2)–H and/or C(5)–H]. *Anal.* Calcd for $C_{15}H_{18}N_4O_5$: C, 53.88; H, 5.43; N, 16.76. Found: C, 53.97; H, 5.56; N, 16.53.

**Reaction of 1 with Phenol or *o*-Cresol in the Presence of $Et_3OBF_4$**——A solution of 1 mmol of **1** and 3 mmol of $Et_3OBF_4$ in 5 ml of $CH_2Cl_2$ was allowed to stand for 24 h, then a solution of 3 mmol of phenol or

*o*-cresol dissolved in 20 ml of $CH_2Cl_2$ was added and the mixture was stirred at room temperature for a further 24 h. The $CH_2Cl_2$ solution was washed with water (20 ml × 5), dried over $Na_2SO_4$, and concentrated. The residue was purified by recrystallization.

**Diethyl 2-(4-Oxo-2,5-cyclohexadienylidene)-3-(4-cyano-5(1*H*)-pyrazolylethylamino)methylenesuccinate(3)**——59.0% yield. mp 172—173°C (benzene). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3400 (NH), 2220 (CN), 1750, 1730, 1700 (CO). PMR (DMSO-$d_6$) $\delta$: 1.00—1.43 (9H, m, 2 × $CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 3.80—4.30 (6H, m, 2 × $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.63 and 6.80 (each 2H, each d, $J$ = 9 Hz,  ), 7.75 (1H, s, =CH), 8.02 (1H, s, pyrazole ring-H), 9.47 (1H, s, NH). *Anal.* Calcd for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.63; H, 5.22; N, 13.77.

**Diethyl 2-(3-Methyl-4-oxo-2,5-cyclohexadienylidene)-3-(4-cyano-5(1*H*)-pyrazolylethylamino)methylenesuccinate (4)**——43% yield. mp 166—167°C (EtOH–$H_2O$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3360 (NH), 2220 (CN), 1760, 1700 (CO). PMR (DMSO-$d_6$) $\delta$: 1.03—1.43 (9H, m, 2 × $CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 2.07 (3H, s, $CH_3$), 3.90—4.33 (6H, m, 2 × $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.58—7.05 (3H, m,  ), 7.80 (1H, s, =CH), 8.06 (1H, s, pyrazole ring-H), 9.42 (1H, s, NH). *Anal.* Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.10; H, 5.91; N, 13.19.

**7-(*p*-Acetoxyphenyl)-6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (5)**——One drop of conc. $H_2SO_4$ was added to a suspension of 1 mmol of **3** in 10 ml of acetic anhydride, and the mixture was stirred for 10 h at 40°C. The solution was poured into ice-water, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and dried over $Na_2SO_4$. After removal of the solvent by evaporation, the residue was recrystallized from *n*-hexane to give 450 mg (100%) of **5** as colorless needles of mp 72—74°C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2220 (CN), 1760, 1690 (CO). PMR (DMSO-$d_6$) $\delta$: 1.05—1.45 (9H, m, 2 × $CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 2.24 (3H, s, $OCOCH_3$), 3.85—4.32 (6H, m, 2 × $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 7.02 and 7.22 (each 2H, each d, $J$ = 9 Hz, Ar–H), 7.80 [1H, s, C(5)–H], 8.06 [1H, s, C(2)–H]. MS *m/z*: 452 ($M^+$). *Anal.* Calcd for $C_{23}H_{24}N_4O_6 \cdot 1/2C_6H_{14}$: C, 63.01; H, 6.31; N, 11.31. Found: C, 63.13; H, 6.30; N, 11.22.

**3′-Cyano-6′-ethoxycarbonyl-4′-ethyl-5-methylspiro{benzo[*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one (6)**——From 1 mmol of **1** and 3 mmol of *p*-cresol, 124 mg of **6** (Table I) was obtained by the method described for the preparation of **3**. PMR (DMSO-$d_6$) $\delta$: 1.08 (3H, t, $J$ = 7 Hz, $CO_2CH_2C\underline{H}_3$), 1.42 (3H, t, $J$ = 7 Hz, $NCH_2C\underline{H}_3$), 2.24 (3H, s, $CH_3$), 3.87—4.25 (4H, m, $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 7.05—7.30 (3H, m, Ar–H), 8.01 and 8.05 [each 1H, each s, C(2′)-H and/or C(5′)-H]. UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 323 (3.19).

**3′-Cyano-6′-ethoxycarbonyl-4′-ethyl-6-methylspiro{benzo[*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one (7)**——A solution of **1** and 3 mmol of *m*-cresol dissolved in 20 ml of $CH_2Cl_2$ was added to a prereacted solution of 1 mmol of **1** and 3 mmol of $Et_3OBF_4$ in 5 ml of $CH_2Cl_2$, and the mixture was refluxed for 3 d. The $CH_2Cl_2$ solution was washed with water (20 ml × 5), dried over $Na_2SO_4$ and concentrated. A small amount of EtOH was added to the residue and the resulting crystalline solid was collected by filtration and purified by recrystallization to give 25 mg of **7** (Table I). PMR (DMSO-$d_6$) $\delta$: 1.08 (3H, t, $J$ = 7 Hz, $CO_2CH_2C\underline{H}_3$), 1.40 (3H, t, $J$ = 7 Hz, $NCH_2C\underline{H}_3$), 2.36 (3H, s, $CH_3$), 3.85—4.25 (4H, m, $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.90—7.25 (3H, m, Ar–H), 8.01 and 8.05 [each 1H, each s, C(2′)-H and/or C(5′)-H].

**3′-Cyano-6′-ethoxycarbonyl-4′-ethyl-5-methoxyspiro{benzo[*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one (8)**——From 1 mmol of **1** and 3 mmol of *p*-methoxyphenol, 60 mg of **8** (Table I) was obtained by the method described for the preparation of **7**. PMR (DMSO-$d_6$) $\delta$: 1.08 (3H, t, $J$ = 7 Hz, $CO_2CH_2C\underline{H}_3$), 1.40 (3H, t, $J$ = 7 Hz, $NCH_2C\underline{H}_3$), 3.68 (3H, s, $OCH_3$), 3.85—4.26 (4H, m, $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.88—7.32 (3H, m, Ar–H), 8.02 and 8.03 [each 1H, each s, C(2′)-H and/or C(5′)-H].

**3′-Cyano-4,6-dimethyl-6′-ethoxycarbonyl-4′-ethylspiro{benzo[*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one (9)**——From 1 mmol of **1** and 3 mmol of 3,5-xylenol, 246 mg of **9** (Table I) was obtained by the method described for the preparation of **3**. PMR (DMSO-$d_6$) $\delta$: 1.11 (3H, t, $J$ = 7 Hz, $CO_2CH_2C\underline{H}_3$), 1.40 (3H, t, $J$ = 7 Hz, $NCH_2C\underline{H}_3$), 1.86 and 2.32 (each 3H, each s, 2 × $CH_3$), 3.90—4.30 (4H, m, $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.76 and 6.96 (each 1H, each s, Ar–H), 8.04 and 8.07 [each 1H, each s, C(2′)–H and/or C(5′)–H].

**Reaction of 1 with α-Naphthol in the Presence of $Et_3OBF_4$**——A solution of 9 mmol of α-naphthol dissolved in 50 ml of $CH_2Cl_2$ was added to a prereacted solution of 3 mmol of **1** and 9 mmol of $Et_3OBF_4$ in 10 ml of $CH_2Cl_2$, and the mixture was stirred at room temperature for 24 h. The $CH_2Cl_2$ solution was washed with water (30 ml × 5), dried over $Na_2SO_4$ and concentrated. EtOH was added to the residue and the resulting precipitate was collected by filtration. Recrystallization gave 738 mg of pure 3′-cyano-6′-ethoxycarbonyl-4′-ethylspiro{naphtho[1,2-*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one (**10**) (Table I). PMR (DMSO-$d_6$) $\delta$: 1.00 (3H, t, $J$ = 7 Hz, $CO_2CH_2C\underline{H}_3$), 1.45 (3H, t, $J$ = 7 Hz, $NCH_2C\underline{H}_3$), 3.95 (2H, q, $J$ = 7 Hz, $CO_2C\underline{H}_2CH_3$), 4.14 (2H, q, $J$ = 7 Hz, $NC\underline{H}_2CH_3$), 7.33—8.10 (6H, m, Ar–H), 8.02 and 8.12 [each 1H, each s, C(2′)–H and/or C(5′)–H]. The filtrate was concentrated *in vacuo*, and the residue was subjected to silica gel column chromatography. The first fraction eluted with $CHCl_3$ gave 33 mg (2.6%) of ethyl α-(1,2-dihydro-1-oxo-2-

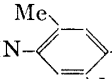
naphthylidenemethyl)-2-oxo-$\Delta^{3(2H),\alpha}$-naphtho[1,2-*b*]furanacetate (**11**) as colorless needles of mp 231—232°C (EtOH). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1810, 1710, 1660 (CO). PMR (DMSO-$d_6$) $\delta$: 1.01 (3H, t, $J$=7 Hz, $CO_2CH_2C\underline{H}_3$), 3.97 (2H, q, $J$=7 Hz, $CO_2C\underline{H}_2CH_3$), 6.75 and 7.30 (each 1H, each d, $J$=9 Hz, CH=CH), 7.55—8.35 (10H, m, Ar–H), 8.48 (1H, s, CH). MS *m/z*: 422 ($M^+$). *Anal.* Calcd for $C_{27}H_{18}O_5$: C, 76.77; H, 4.30. Found: C, 76.63; H, 4.23.

**3′-Cyano-6′-ethoxycarbonyl-4′-ethylspiro{naphtho[2,1-*b*]furan-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one (12)**——From 1 mmol of **1** and 3 mmol of $\beta$-naphthol, 256 mg of **12** (Table I) was obtained by the method described for the preparation of **3**. PMR (DMSO-$d_6$) $\delta$: 1.03 (3H, t, $J$=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.51 (3H, t, $J$=7 Hz, $NCH_2C\underline{H}_3$), 3.95 (2H, q, $J$=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.26 (2H, q, $J$=7 Hz, $NC\underline{H}_2CH_3$), 7.15—8.10 (6H, m, Ar–H), 8.00 and 8.20 [each 1H, each s, C(2′)–H and/or C(5′)–H].

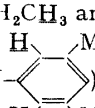
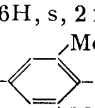
**6,7-Bis(ethoxycarbonyl)-4,7-dihydro-4-ethyl-7-(4-ethylaminophenyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (13)**——From 1 mmol of **1** and 3 mmol of aniline, 250 mg (57.2%) of **13** (Table II) was obtained by the method described for the preparation of **3**. PMR (DMSO-$d_6$) $\delta$: 0.95—1.45 (12H, m, 2×$CO_2CH_2C\underline{H}_3$ and 2×$NCH_2C\underline{H}_3$), 3.80—4.26 (8H, m, 2×$CO_2C\underline{H}_2CH_3$ and 2×$NC\underline{H}_2CH_3$), 6.37 and 6.88 (each 2H, each d, $J$=9 Hz, Ar–H), 7.70 [1H, s, C(5)–H], 7.96 [1H, s, C(2)–H].

**6,7-Bis(ethoxycarbonyl)-4,7-dihydro-7-{4-(*N*,*N*-dimethylamino)phenyl}-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (14)**——After usual work-up of 1 mmol of **1** and 3 mmol of *N*,*N*-dimethylaniline in the presence of $Et_3OBF_4$, the residual oil was subjected to silica gel column chromatography. The first fraction eluted with $CHCl_3$ provided 85 mg (19.5%) of **14** (Table II). PMR (DMSO-$d_6$) $\delta$: 1.03—1.40 (9H, m, 2×$CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 2.84 (6H, s, 2×$CH_3$), 3.85—4.26 (6H, m, 2×$CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.55 and 6.98 (each 2H, each d, $J$=9 Hz, Ar–H), 7.74 [1H, s, C(5)–H], 8.00 [1H, s, C(2)–H].

**7-(4-Amino-3-methylphenyl)-6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (15)**——From 1 mmol of **1** and 3 mmol of *o*-toluidine, 139 mg (32.8%) of **15** (Table II) was obtained by the method described for the preparation of **14**. PMR (DMSO-$d_6$) $\delta$: 1.00—1.42 (9H, m, 2×$CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 1.96 (3H, s, $CH_3$), 3.83—4.26 (6H, m, 2×$CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 4.84 (2H, s, $NH_2$), 6.35—6.83 (3H, m, Ar–H), 7.70 [1H, s, C(5)–H], 7.96 [1H, s, C(2)–H].

**Reaction of 1 with 2,5-Xylidine in the Presence of $Et_3OBF_4$**——A solution of 3 mmol of 2,5-xylidine dissolved in 20 ml of $CH_2Cl_2$ was added to a prereacted solution of 1 mmol of **1** and 3 mmol of $Et_3OBF_4$ in 5 ml of $CH_2Cl_2$, and the mixture was stirred at room temperature for 24 h. After usual work-up, an oily material was obtained and subjected to silica gel column chromatography. The first fraction eluted with $CHCl_3$ provided 31 mg (7.1%) of 6,7-bis(ethoxycarbonyl)-4,7-dihydro-7-(2,5-dimethylanilino)-4-ethylpyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (**19**) (Table II). PMR (DMSO-$d_6$) $\delta$: 1.02—1.52 (9H, 2×$CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 2.06 and 2.10 (each 3H, each s, 2×$CH_3$), 3.95—4.30 (6H, m, 2×$CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 5.70 (1H, br s, –HN–  ), 5.78 (1H, s, NH), 6.46 (1H, bd, $J$=9 Hz, –HN–  ), 6.88 (1H, d, $J$=9 Hz, –HN–  ), 7.95 and 8.02 [each 1H, each s, C(2)–H and/or C(5)–H]. The second fraction eluted with $CHCl_3$ gave 70 mg (14.6%) of 6,7-bis(ethoxycarbonyl)-4,7-dihydro-7-(2,5-dimethyl-4-ethylaminophenyl)-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**16**) (Table II). PMR (DMSO-$d_6$) $\delta$: 0.92—1.42 (12H, m, 2×$CO_2CH_2C\underline{H}_3$ and 2×$NCH_2C\underline{H}_3$), 1.67 and 2.03 (each 3H, each s, 2×$CH_3$), 3.77—4.28 (8H, m, 2×$CO_2C\underline{H}_2CH_3$ and 2×$NC\underline{H}_2CH_3$), 6.16 and 7.04 (each 1H, each s, Ar–H), 7.66 [1H, s, C(5)–H], 7.88 [1H, s, C(2)–H].

**6,7-Bis(ethoxycarbonyl)-4,7-dihydro-4-ethyl-7-(*p*-methoxyanilino)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (17)**——A solution of 3 mmol of *p*-anisidine dissolved in 20 ml of $CH_2Cl_2$ was added to a prereacted solution of 1 mmol of **1** and 3 mmol of $Et_3OBF_4$ in 5 ml of $CH_2Cl_2$, and the mixture was stirred at room temperature for 10 min. After usual work-up, 318 mg (72.3%) of **17** (Table II) was obtained. PMR (DMSO-$d_6$) $\delta$: 1.00—1.35 (9H, m, 2×$CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 3.64 (3H, s, $OCH_3$), 3.80—4.35 (6H, m, 2×$CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 5.70 (1H, s, NH), 6.34 and 6.66 (each 2H, each d, $J$=9 Hz, Ar–H), 7.77 [1H, s, C(5)–H], 8.06 [1H, s, C(2)–H].

**6,7-Bis(ethoxycarbonyl)-4,7-dihydro-7-(3,5-dimethylanilino)-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (18)**——A solution of 3 mmol of 3,5-xylidine dissolved in 20 ml of $CH_2Cl_2$ was added to a prereacted solution of 1 mmol of **1** and 3 mmol of $Et_3OBF_4$ in 5 ml of $CH_2Cl_2$, and the mixture was stirred at room temperature for 2 h. After usual work-up, 206 mg (47.2%) of **18** (Table II) was obtained. PMR (DMSO-$d_6$) $\delta$: 1.03—1.45 (9H, m, 2×$CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 2.09 (6H, s, 2×$CH_3$), 3.95 (6H, m, 2×$CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.00 (3H, s, –<u>H</u>N–  ), 6.39 (1H, s, –HN–  ), 7.92 and 8.02 [each 1H, each s, C(2)–H and/or C(5)–H].

**7-(*p*-Chloroanilino)-6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (20)**——From 1 mmol of **1** and 3 mmol of *p*-chloroaniline, 289 mg (65.1%) of **20** (Table II) was obtained

by the method described for the preparation of **17**. PMR (DMSO-$d_6$) $\delta$: 1.02—1.43 (9H, m, $2\times CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 3.96—4.27 (6H, m, $2\times CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.43 and 7.06 (each 2H, each d, $J$= 9 Hz, Ar–H), 7.48 (1H, s, NH), 7.92 and 8.03 [each 1H, each s, C(2)–H and/or C(5)–H].

**6,7-Bis(ethoxycarbonyl)-4,7-dihydro-4-ethyl-7-(*p*-nitroanilino)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile** (**21**)——From 1 mmol of **1** and 3 mmol of *p*-nitroaniline, 279 mg (61.3%) of **20** (Table II) was obtained by the method described for the preparation of **17**. PMR (DMSO-$d_6$) $\delta$: 1.03—1.30 (6H, m, $2\times CO_2CH_2C\underline{H}_3$), 1.48 (3H, t, $J$=7 Hz, $NCH_2C\underline{H}_3$), 3.97—4.38 (6H, m, $2\times CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.67 and 7.95 (each 2H, each d, $J$=9 Hz, Ar–H), 7.77 (1H, s, NH), 8.10 and 8.12 [each 1H, each s, C(2)–H and/or C(5)–H].

**Reaction of 1 with p-Toluidine in the Presence of $Et_3OBF_4$**——A solution of 9 mmol of *p*-toluidine dissolved in 50 ml of $CH_2Cl_2$ was added to a prereacted solution of 3 mmol of **1** and 9 mmol of $Et_3OBF_4$ in 10 ml of $CH_2Cl_2$, and the mixture was refluxed for 5 h. After usual work-up, the residual oil obtained was subjected to silica gel column chromatography. The first fraction eluted with $CHCl_3$ provided 90 mg (8.0%) of 3-cyano-11*b*-ethoxycarbonyl-4-ethyl-10-methyl-4,6,7,11*b*-tetrahydropyrazolo[1′,5′: 1,2]pyrimido[5,6-*c*]quinolin-6-one (**23**) as colorless needles of mp 240—242°C (EtOH). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3280 (NH), 2220 (CN), 1740, 1680 (CO). PMR (DMSO-$d_6$) $\delta$: 0.97 (3H, t, $J$=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.31 (3H, t, $J$=7 Hz, $NCH_2C\underline{H}_3$), 2.26 (3H, s, $CH_3$), 3.85—4.18 (4H, m, $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.90 [1H, d, $J$=9 Hz, C(8)–H], 7.15 [1H, br d, $J$= 9 Hz, C(9)–H], 7.66 [1H, s, C(2)–H], 8.24 [2H, s, C(5)–H and C(11)–H]. 10.48 (1H, s, NH). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 338 (2.80). *Anal.* Calcd for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.46; H, 5.03; N, 18.64. The second fraction eluted with $CHCl_3$ gave 225 mg (19.9%) of 3′-cyano-6′-ethoxycarbonyl-4′-ethyl-5-methylspiro{indole-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one (**22**) as colorless needles of mp 243—246°C (EtOH). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3220 (NH), 2220 (CN), 1730, 1700 (CO). PMR (DMSO-$d_6$) $\delta$: 1.03 (3H, t, $J$=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.37 (3H, t, $J$=7 Hz, $NCH_2C\underline{H}_3$), 2.16 (3H, s, $CH_3$), 3.75—4.20 (4H, m, $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.63—7.12 (3H, m, Ar–H), 7.87 [2H, s, C(2′)–H and C(5′)–H], 10.68 (1H, s, NH). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 324 (3.08). *Anal.* Calcd for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.35; H, 5.02; N, 18.44.

**3′-Cyano-6′-ethoxycarbonyl-4-ethyl-6-methylspiro{indole-3(2*H*),7′(4′*H*)-pyrazolo[1,5-*a*]pyrimidin}-2-one** (**24**)——From 1 mmol of **1** and 3 mmol of *m*-toluidine, 149 mg (39.4%) of **24** was obtained by the method described for the preparation of **22**. This product was recrystallized from EtOH to give an analytical sample of mp 235—237°C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3260 (NH), 2220 (CN), 1740, 1690 (CO). PMR (DMSO-$d_6$) $\delta$: 1.05 (3H, $J$=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.38 (3H, t, $J$=7 Hz, $NCH_2C\underline{H}_3$), 2.30 (3H, s, $CH_3$), 3.80—4.30 (4H, m, $CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 6.67—7.02 (3H, m, Ar–H), 7.91 and 7.93 [each 1H, each s, C(2′)–H and/or C(5′)–H], 10.64 (1H, s, NH). *Anal.* Calcd for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.70; H, 4.83; N, 18.48.

**6,7-Bis(ethoxycarbonyl)-4,7-dihydro-4-ethyl-7-(8-hydroxy-5-quinolyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile** (**25**)——A solution of 3 mmol of 8-hydroxyquinoline dissolved in 20 ml of $CH_2Cl_2$ was added to a prereacted solution of 1 mmol of **1** and 3 mmol of $Et_3OBF_4$ in 5 ml of $CH_2Cl_2$, and the mixture was stirred at room temperature for 6 d. After usual work-up, the crude crystalline solid was recrystallized from EtOH to give 85 mg (18.4%) of **25** as colorless needles of mp 210—213°C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3340 (OH), 2220 (CN), 1750, 1690 (CO). PMR (DMSO-$d_6$) $\delta$: 0.96—1.26 (6H, m, $2\times CO_2CH_2C\underline{H}_3$), 1.43 (3H, t, $J$=7 Hz, $NCH_2C\underline{H}_3$), 3.83—4.36 (6H, m, $2\times CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 7.26—8.86 (5H, m, Ar–H), 7.76 and 7.86 [each 1H, each s, C(2)–H and/or C(5)–H]. $FeCl_3$ test: positive (dark green). *Anal.* Calcd for $C_{24}H_{23}N_5O_5$: C, 62.46; H, 5.02; N, 15.18. Found: C, 62.26; H, 5.22; N, 15.19.

**7-(2-Benzo[*b*]furanyl)-6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile** (**26**)——From 1 mmol of **1** and 3 mmol of benzo[*b*]furan, 206 mg (47.4%) of **26** was obtained by the method described for the preparation of **3**. This product was recrystallized from AcOEt–*n*-hexane mixture to give an analytical sample of mp 167°C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2220 (CN), 1760, 1690 (CO). PMR (DMSO-$d_6$) $\delta$: 1.08—1.52 (9H, m, $2\times CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 3.95—4.38 (6H, m, $2\times CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 7.10 [1H, s, C(3)–H of benzo[*b*]furan], 7.10—7.70 (4H, m, Ar–H), 7.90 and 8.02 [each 1H, each s, C(2)–H and/or C(5)–H]. *Anal.* Calcd for $C_{23}H_{22}N_4O_5$: C, 63.58; H, 5.10; N, 12.90. Found: C, 63.83; H, 5.26; N, 12.94.

**7-Acetonyl-6,7-bis(ethoxycarbonyl)-4,7-dihydro-4-ethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile** (**27**)——A prereacted solution of 1 mmol of **1** and 3 mmol of $Et_3OBF_4$ in 5 ml of $CH_2Cl_2$ was concentrated *in vacuo* and the residual oil was dissolved in 20 ml of acetone. Five mmol of $K_2CO_3$ was added, and the mixture was refluxed for 5 h. After removal of the solvent by evaporation, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over $Na_2SO_4$ and concentrated. The residual oil was subjected to silica gel column chromatography. The first fraction eluted with $CHCl_3$ provided 161 mg (43.1%) of **27** as colorless needles of mp 122—123°C (AcOEt–*n*-hexane). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2220 (CN), 1740, 1710, 1690 (CO). PMR (DMSO-$d_6$) $\delta$: 0.98—1.42 (9H, m, $2\times CO_2CH_2C\underline{H}_3$ and $NCH_2C\underline{H}_3$), 1.95 (3H, s, $COCH_3$), 3.41 and 3.69 (2H, ABq, $J$=17 Hz, $C\underline{H}_2COCH_3$), 3.85—4.25 (6H, m, $2\times CO_2C\underline{H}_2CH_3$ and $NC\underline{H}_2CH_3$), 7.69 [1H, s, C(5)–H], 7.96 [1H, s, C(2)–H]. *Anal.* Calcd for $C_{18}H_{22}N_4O_5$: C, 57.74; H, 5.92; N, 14.97. Found: C, 57.99; H, 5.69; N, 15.10.

**Acknowledgement** We are grateful to Dr. S. Matsunaga and Dr. A. Numata for the measurements of MS and PMR spectra and to Mrs. Y. Tsukamoto for elemental analyses. We are also indebted to Miss U. Shimada for her skillful technical assistance.

## References and Notes

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7) In the cases of aniline and 2,5-xylidine, 7-*p*-aminophenyl adducts (**13** and **16**) with *N*-ethylation were isolated.
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