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Studies on Ketene and Its Derivatives. XCVI.[1] Synthesis of Pyrido[2,1-*b*]benzoazoles

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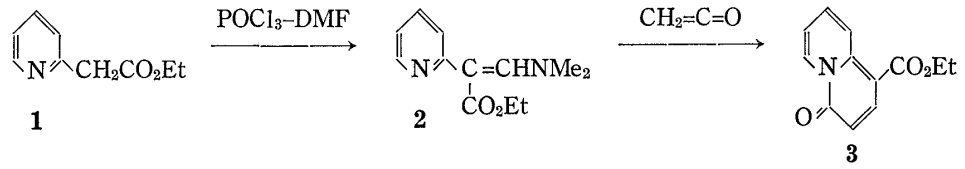
Vilsmeier reactions of ethyl 2-benzimidazoleacetate (**4**), ethyl 2-benzothiazoleacetate (**5**), and ethyl 2-benzoxazoleacetate (**6**) gave ethyl α-(dimethylaminomethylene)-2-benzimidazoleacetate (**7**), ethyl α-(dimethylaminomethylene)-2-benzothiazoleacetate (**8**), and ethyl α-(dimethylaminomethylene)-2-benzoxazoleacetate (**9**), respectively.

Reaction of the enamines (**7**, **8** and **9**) with diketene, acetic anhydride, propionic anhydride, and active methylene compounds such as ethyl cyanoacetate and malononitrile gave rise to the corresponding pyrido[2,1-*b*]benzoazoles (**10**—**19**).

Keywords——ethyl 2-benzoazoleacetates; ethyl α-(dimethylaminomethylene)-2-benzoazoleacetates; pyrido[2,1-*b*]benzoazoles; diketene; acid anhydrides; malononitrile; ethyl cyanoacetate; Vilsmeier reaction

Previously, we[3] reported that the reaction of ethyl 2-pyridineacetate (**1**) with a Vilsmeier reagent gave the enamine, ethyl α-(dimethylaminomethylene)-2-pyridineacecate (**2**), which reacted with ketene giving ethyl 4-oxo-4*H*-quinolizine-1-carboxylate (**3**). The reaction might well involve 1,4-dipolar cycloaddition of ketene to the enamine (**2**) accompanied by the elimination of dimethylamine to give the quinolizine (**3**). Similar reactions with diketene, acid anydrides, and active methylene compounds such as ethyl acetoacetate, ethyl cyanoacetate, and diethyl malonate were reported to give the corresponding quinolizine derivatives.[4] As a continuation of this study, we have investigated the synthesis of pyrido[2,1-*b*]-benzoazole derivatives (**12**—**18**) from the enamines (**7**—**9**) prepared by the Vilsmeier reaction of the benzoazole acetates (**4**—**6**).



1 **2** **3**

Chart 1

The benzoazoles used in the reaction were ethyl 2-benzimidazoleacetate (**4**), ethyl 2-benzothiazoleacetate (**5**), and ethyl 2-benzoxazoleacetate (**6**).

When the acetate (**4**) was allowed to react with the Vilsmeier reagent prepared from phosphorus oxychloride ($POCl_3$) and dimethylformamide (DMF), ethyl α-(dimethylaminomethylene)-2-benzimidazoleacetate (**7**) was obtained in 66% yield. Similarly, the acetates (**5** and **6**) reacted with the Vilsmeier reagent to give the corresponding enamines, ethyl α-(dimethylaminomethylene)-2-benzothiazoleacetate (**8**) and ethyl α-(dimethylaminomethylene)-2-benzoxazoleacetate (**9**) in 78 and 69% yields, respectively. Structure assignments of these products were made on the basis of elemental analyses and spectral data.

1) Part XCV: T. Kato, Y. Suzuki, and M. Sato, *Chem. Pharm. Bull.* (Tokyo), **27**, 1181 (1979).
2) Location: *Aobayama, Sendai 980, Japan.*
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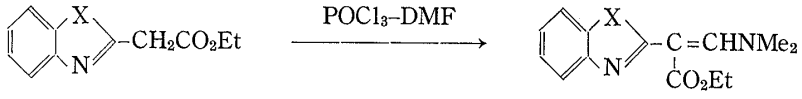
4) T. Kato, T. Chiba, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **22**, 744 (1974).



4: X=NH
5: X=S
6: X=O

7: X=NH
8: X=S
9: X=O

Chart 2

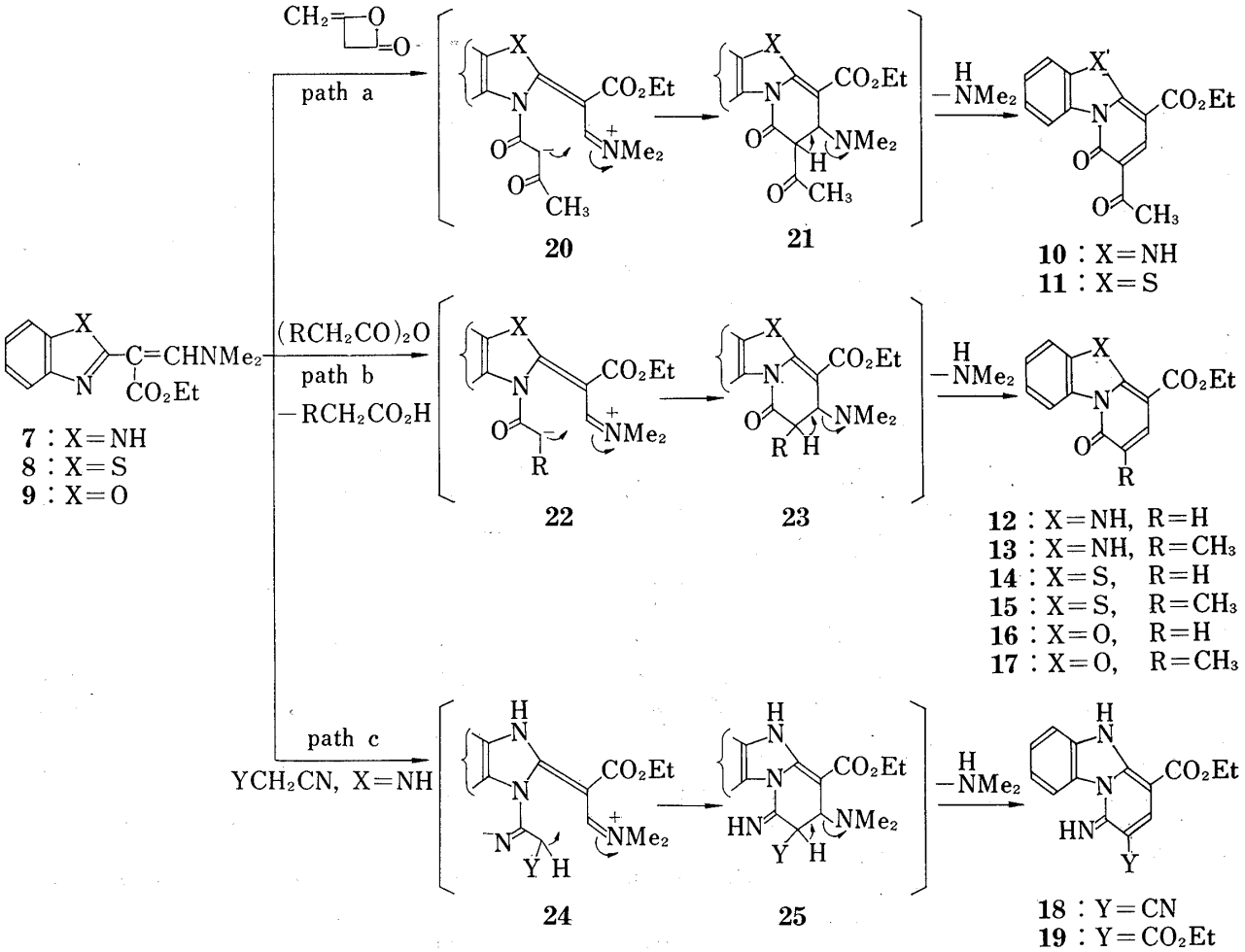
The enamine (**7**) was heated with diketene in chloroform to give the tricyclic compound, ethyl 2-acetyl-1-oxo-1*H*,5*H*-pyrido[2,1-*b*]benzimidazole-4-carboxylate (**10**) in 81% yield. Similarly, reaction of the enamine (**8**) with diketene gave rise to ethyl 2-acetyl-1-oxo-1H-pyrido[2,1-*b*]benzothiazole-4-carboxylate (**11**) in 89% yield. However, reaction of the oxazole derivative (**9**) with diketene resulted in the recovery of the starting enamine (**9**).

Heating of the benzimidazole enamine (**7**) with acetic anhydride gave tricyclic compound, ethyl 1-oxo-1*H*,5*H*-pyrido[2,1-*b*]benzimidazole-4-carboxylate (**12**) in 86% yield. Similar reaction of **7** with propionic anhydride gave the 2-methyl compound (**13**) in 90% yield.

Similarly, the benzothiazole enamine (**8**) reacted with acetic anhydride and propionic anhydride to give tricyclic compounds, ethyl 1-oxo-1*H*-pyrido[2,1-*b*]benzothiazole-4-carboxylate (**14**) and the 2-methyl derivative (**15**) in 62 and 70% yields, respectively.

The pyrido[2,1-*b*]benzoxazole derivatives (**16** and **17**) were prepared by heating the benzoxazole enamine (**9**) with acetic anhydride and propionic anhydride.

Lastly, reactions with active methylene compounds such as malononitrile and ethyl cyanoacetate were carried out. Though the benzothiazole and benzoxazole enamines (**8** and



7 : X=NH
8 : X=S
9 : X=O

10 : X=NH
11 : X=S

12 : X=NH, R=H
13 : X=NH, R=CH3
14 : X=S, R=H
15 : X=S, R=CH3
16 : X=O, R=H
17 : X=O, R=CH3

18 : Y=CN
19 : Y=CO2Et

Chart 3

9) did not react, the benzimidazole enamine (7) reacted with malononitrile and ethyl cyanoacetate to give the corresponding 1-imino-1*H*-pyrido[2,1-*b*]benzimidazole derivatives (18 and 19).

Elemental analyses and spectral data of these products were consistent with the tricyclic structures (12—19).

The formations of the tricyclic compounds can be rationalized as follows; addition of diketene to the ring nitrogen of the enamine would form the dipolar intermediate (20), which is transformed into the cycloadduct (21). Elimination of dimethylamine from 21 gives the products (10 and 11) (path a).

Similarly, acylation with acid anhydrides by path b gives the N-acyl intermediates (22), cyclization of which, accompanied by elimination of dimethylamine, gives the products (12—17).

Addition of the enamine 7 to active methylene compounds with prototropy would yield the cycloadducts (25) as intermediates, which are then transformed to the products (18 and 19) (path c).

Experimental

Infrared (IR) spectra were taken with a JASCO IR-S spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured with Hitachi R-20 and JEOL-JNM-PS-100 instruments using tetramethylsilane as an internal standard. Melting points are uncorrected.

Ethyl α-(Dimethylaminomethylene)-2-benzimidazoleacetate (7)——To a Vilsmeier reagent prepared from $POCl_3$ (3.1 g, 20 mmol) and DMF (2.2 g, 30 mmol), ethyl 2-benzimidazoleacetate (4)[5] (2 g, 10 mmol) was added with stirring. After heating on a water bath at 95° for 30 min, the reaction mixture was poured into ice-cold water (30 ml) and made alkaline with K_2CO_3. The mixture was extracted with $CHCl_3$ (3×20 ml). The $CHCl_3$ solution was dried over K_2CO_3 and then condensed to dryness. The resulting material was recrystallized from ethyl acetate to give 1.7 g (66%) of colorless needles (7): mp 199—200°. *Anal.* Calcd. for $C_{14}H_{17}N_3O_2$ (7): C, 64.84; H, 6.68; N, 16.21. Found: C, 64.71; H, 6.68; N, 15.98. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 1660, 1610. NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 3.02 (6H, s, $N(CH_3)_2$), 4.26 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.21 (1H, s, $=\underline{CH}$–NMe_2), 7.06—7.70 (4H, m, aromatic H), 7.92 (1H, br, NH).

Ethyl α-(Dimethylaminomethylene)-2-benzothiazoleacetate (8)——Following the method given for the enamine (7), ethyl 2-benzothiazoleacetate (5)[6] (2.21 g, 10 mmol) was treated with a Vilsmeier reagent prepared from $POCl_3$ (3.1 g) and DMF (2.2 g) to give 2.15 g(78%) of colorless needles (8) (from *n*-hexane): mp 72—73°. *Anal.* Calcd. for $C_{14}H_{16}N_2O_2S$ (8): C, 60.85; H, 5.84; N, 10.14; S, 11.60. Found: C, 61.04; H, 5.90; N, 10.26; S, 11.51. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685, 1615. NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 3.02 (6H, s, $-N(CH_3)_2$), 4.30 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.35—7.60 (2H, m, aromatic H), 7.90—8.20 (3H, m, aromatic H and $=\underline{CH}$–$N(CH_3)_2$).

Ethyl α-(Dimethylaminomethylene)-2-benzoxazoleacetate (9)——Similar treatment of ethyl 2-benzoxazoleacetate (6)[6] (2.1 g, 10 mmol) with the Vilsmeier reagent (from DMF, 2.2 g and $POCl_3$ 3.1 g) gave 1.8 g (69%) of colorless plates (9) (from cyclohexane): mp 115—116°. *Anal.* Calcd. for $C_{14}H_{16}N_2O_3$ (9): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.68; H, 6.15; N, 10.72. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1618. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.85 (6H, s, $N(CH_3)_2$), 4.18 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.20—7.60 (4H, m, aromatic H), 7.67 (1H, s, $-\underline{CH}$–NMe_2).

Ethyl 2-Acetyl-1-oxo-1*H*,5*H*-pyrido[2,1-*b*]benzimidazole-4-carboxylate (10)——A solution of 7 (1.3 g, 5 mmol) and diketene (0.84 g, 10 mmol) in $CHCl_3$ (10 ml) was refluxed for 4 hr. The reaction mixture was evaporated to dryness. The crystalline residue was washed with benzene and purified by recrystallization from ethanol to give 1.2 g (81%) of colorless needles (10): mp 280° (dec.). *Anal.* Calcd. for $C_{16}H_{14}N_2O_4$ (10); C, 64.42; H, 4.73; N, 9.39. Found: C, 64.41; H, 4.77; N, 9.38. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3160, 1695, 1670, 1635. NMR (CF_3CO_2H) δ: 1.53 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.93 (3H, s, $CO\underline{CH_3}$), 4.66 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.67—8.01 (3H, m, 6-, 7- and 8-H), 8.06—8.99 (1H, m, 9-H), 9.13 (1H, s, 3-H).

Ethyl 2-Acetyl-1-oxo-1*H*-pyrido[2,1-*b*]benzothiazole-4-carboxylate (11)——A solution of 8 (1.4 g, 5 mmol) and diketene (0.84 g, 0.10 mmol) in benzene (10 ml) in the presence of a catalytic amount of triethylamine was allowed to stand overnight at room temperature. The reaction mixture was evaporated down *in vacuo*. After washing with *n*-hexane, the residue was recrystallized from ethyl acetate to give 1.4 g (89%) of colorless needles (11): mp 211—212°. *Anal.* Calcd. for $C_{16}H_{13}NO_4S$ (11): C, 60.94; H, 4.16; N, 4.44; S,

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6) A.E. von Dormael, *J. Nys. Chem. Ind.*, **63**, 483 (1950).

10.17. Found: C, 61.07; H, 4.14; N, 4.44; S, 9.90. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705, 1677, 1650. NMR ($CDCl_3$) δ: 1.50 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.88 (3H, s, $CO\underline{CH_3}$), 4.55 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.60—8.10 (3H, m, 6-, 7- and 8-H), 9.03 (1H, s, 3-H), 9.27—9.50 (1H, m, 9-H).

Ethyl 1-Oxo-1*H*,5*H*-pyrido[2,1-*b*]benzimidazole-4-carboxylate (12)——A suspension of **7** (0.26 g, 1 mmol) in acetic anhydride (2 ml) was refluxed for 1 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate to give 0.22 g (86%) of colorless plates (**12**): mp 253—255° (dec.). *Anal.* Calcd. for $C_{14}H_{12}N_2O_3$ (**12**): C, 65.62; H, 4.72; N, 10.92. Found: C, 65.90; H, 4.68; N, 10.92. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1690, 1640. NMR (DMSO-d_6) δ: 1.40 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 4.42 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.03 (1H, d, J=10.0 Hz, 2-H), 7.27—7.67 (2H, m, 7- and 8-H), 7.68—7.90 (1H, m, 6-H), 8.05 (1H, d, J=10.0 Hz, 3-H), 8.63—8.87 (1H, m, 9-H), 12.42—12.57 (1H, br, NH).

Ethyl 2-Methyl-1-oxo-1*H*,5*H*-pyrido[2,1-*b*]benzimidazole-4-carboxylate (13)——A suspension of **7** (0.26 g, 1 mmol) in propionic anhydride (2 ml) was refluxed for 1 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate to give 0.12 g (90%) of colorless plates (**13**): mp 230—231°. *Anal.* Calcd. for $C_{15}H_{14}N_2O_3$ (**13**): C, 66.35; H, 5.22; N, 10.37. Found: C, 66.69; H, 5.38; N, 10.33. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1692, 1650. NMR (DMSO-d_6) δ: 1.36 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 3.13 (3H, s, 2-CH_3), 4.38 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.38—7.68 (2H, m, 7- and 8-H), 7.70—7.85 (1H, m, 6-H), 7.93 (1H, s, 3-H), 8.68—8.88 (1H, m, 9-H), 12.40—12.55 (1H, br, NH).

Ethyl 1-Oxo-1*H*-pyrido[2,1-*b*]benzothiazole-4-carboxylate (14)——A suspension of **8** (0.28 g, 1 mmol) in acetic anhydride (2 ml) was refluxed for 4 hr. The reaction mixture was treated as described above to give 0.17 g (62%) of yellow needles (**14**) (from ether): mp 171—172°. *Anal.* Calcd. for $C_{14}H_{11}NO_3S$ (**14**): C, 61.53; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.33; H, 4.00; N, 5.04; S, 11.89. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1702, 1668. NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 4.50 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.58 (1H, d, J=10.0 Hz, 2-H), 7.50—8.05 (3H, m, 6-, 7- and 8-H), 8.17 (1H, d, J=10.0 Hz, 3-H), 9.35—9.60 (1H, m, 9-H).

Ethyl 2-Methyl-1-oxo-1*H*-pyrido[2,1-*b*]benzothiazole-4-carboxylate (15)——A suspension of **8** (0.28 g, 1 mmol) in propionic anhydride (2 ml) was refluxed for 4 hr. The reaction mixture was treated as described above to give 0.2 g (70%) of yellow needles (**15**) (from ether): mp 179—180°. *Anal.* Calcd. for $C_{15}H_{13}NO_3S$ (**15**): C, 62.70; H, 4.56; N, 4.87; S, 11.16. Found: C, 62.89; H, 4.52; N, 5.04; S, 11.20. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1692, 1649. NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.30 (3H, s, 2-CH_3), 4.45 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.45—7.95 (3H, m, 6-, 7- and 8-H), 8.02 (1H, s, 3-H), 9.30—9.52 (1H, m, 9-H).

Ethyl 1-Oxo-1*H*-pyrido[2,1-*b*]benzoxazole-4-carboxylate (16)——A suspension of **9** (0.26 g, 1 mmol) in acetic anhydride (2 ml) was refluxed for 24 hr. The reaction mixture was treated as described above to give 0.13 g (51%) of colorless needles (**16**) (from ether): mp 152—153°. *Anal.* Calcd. for $C_{14}H_{11}NO_4$ (**16**): C, 65.36; H, 4.31; N, 5.45. Found: C, 65.61; H, 4.19; N, 5.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1690. NMR ($CDCl_3$) δ: 1.50 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 4.50 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.45 (1H, d, J=10.0 Hz, 2-H), 7.37—7.85 (3H, m, 6-, 7- and 8-H), 8.20 (1H, d, J=10.0 Hz, 3-H), 8.48—8.90 (1H, m, 9-H).

Ethyl 2-Methyl-1-oxo-1*H*-pyrido[2,1-*b*]benzoxazole-4-carboxylate (17)——A suspension of **9** (0.26 g, 1 mmol) in propionic anhydride (2 ml) was refluxed for 12 hr. Treatment of the reaction mixture as described above gave 0.16 g (59%) of colorless needles (**17**) (from ether): mp 159—160°. *Anal.* Calcd. for $C_{15}H_{13}NO_4$ (**17**): C, 66.41; H, 4.83; N, 5.16. Found: C, 66.76; H, 4.87; N, 5.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722, 1685. NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 4.45 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 2.25 (3H, s, 2-CH_3), 7.33—7.73 (3H, m, 6-, 7- and 8-H), 8.03 (1H, s, 3-H), 8.50—8.90 (1H, m, 9-H).

Ethyl 2-Cyano-1-imino-1*H*,5*H*-pyrido[2,1-*b*]benzimidazole-4-carboxylate (18)——A mixture of **7** (0.13 g, 0.5 mmol), malononitrile (0.03 g, 0.5 mmol), and triethylamine (0.05 g, 0.5 mmol) in benzene (5 ml) was refluxed for 2 hr. After cooling, the separated crystals were collected by filtration and recrystallized from ethanol to give 0.07 g (50%) of pale yellow needles (**18**); mp 255—258°. *Anal.* Calcd. for $C_{15}H_{12}N_4O_2$ (**18**): C, 64.27; H, 4.32; N, 19.99. Found: C, 64.57; H, 4.39; N, 20.09. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 3260, 2210, 1695, 1625. NMR (CF_3CO_2H) δ: 1.47 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 4.58 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.50—8.20 (4H, m, =NH and 6-, 7- and 8-H), 8.40—8.70 (1H, m, 9-H), 8.80 (1H, s, 3-H).

Diethyl 1-Imino-1*H*,5*H*-pyrido[2,1-*b*]benzimidazole-2,4-dicarboxylate (19)——A mixture of **7** (0.13 g, 0.5 mmol), ethyl cyanoacetate (0.06 g, 0.5 mmol), and triethylamine (0.05 g, 0.5 mmol) in benzene (5 ml) was refluxed for 6 hr. After cooling, the precipitated crystalline mass was collected and purified by recrystallization from ethanol to give 0.09 g (50%) of colorless needles (**19**); mp 223—224°. *Anal.* Calcd. for $C_{17}H_{17}N_3O_4$ (**19**): C, 62.37; H, 5.24; N, 12.84. Found: C, 62.67; H, 5.00; N, 12.96. IR ν_{max}^{KBr} cm^{-1}: 3360, 3240, 1705, 1680, 1620. NMR (CF_3CO_2H) δ: 1.50 (6H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 4.53 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 4.57 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.50—8.20 (3H, m, 6-, 7- and 8-H), 8.30—8.60 (1H, m, 9-H), 8.80—9.50 (1H, br, =NH), 9.33 (1H, s, 3-H).

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