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Intramolecular Reactions of Enaminonitriles. A New Synthesis of β-Aminopyrroles and Related Heterocycles[1)]

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Several new β-aminopyrroles, 3-aminoindoles, pyrido[3,4-*b*]indoles, and pyrrolo[3,2-*b*]pyridines have been synthesized by a sequence of reactions involving intramolecular addition of an enamine to a cyano group. Enamine (**1**), prepared from *tert*-butyl aminocyanoacetate and cyclohexane-1,3-dione, cyclized after substitution of the methine by ethyl bromoacetate in the presence of sodium ethoxide to afford 2-*tert*-butoxycarbonyl-2-ethoxycarbonylmethyl-3-imino-4-oxo-4,5,6,7-tetrahydroindoline (**2**). Reaction of **1** with methyl vinyl ketone-sodium ethoxide furnished 3-amino-2-*tert*-butoxycarbonyl-4-oxo-4,5,6,7-tetrahydroindole (**7**). Similarly, certain 3-aminopyrroles (**44** and **45**) and pyrrolo[3,2-*b*]pyridines (**51** and **52**) have been synthesized from the enamine (**41**) prepared from acetoacetate and *tert*-butyl aminocyanoacetate. Enamines (**70**—**72**) obtained by condensation of ethyl acetoacetate with aminocyanoacetamides underwent cyclizations to 3-amino-2-carbamoylpyrroles (**73**—**75**) upon treatment with base. Several new 3-aminopyrroles thus prepared have been derived into new pyrrolo[3,2-*d*]- (**78**—**81**) and pyrrolo[3,4-*d*]pyrimidines (**90** and **91**). A steric effect of the neighbouring butoxycarbonyl group in **41** has also been briefly discussed.

Keywords——α-aminocyanoacetate; enaminonitriles; β-aminopyrroles; 3-aminoindoles; pyrido[3,2-*b*]indoles; pyrrolo[3,2-*b*]pyridines; pyrrolo[3,4-*d*]pyrimidines; pyrrolo[3,2-*d*]pyrimidines

Previously, we reported syntheses[1a)] of several new β-aminopyrroles, 3-aminoindoles, pyrido[3,2-*b*]indoles, and pyrrolo[3,2-*b*]pyridines, by an intramolecular cyclization of enaminonitriles.[3)] A successful use of certain β-aminopyrroles prepared by this method for the syntheses of new pyrrolo[3,4-*d*]- and pyrrolo[3,2-*d*]pyrimidines was also briefly reported.[1b–d)] The present paper describes the details of these reactions.

Various β-aminopyrroles have been found in nature as exemplified by a series of the "pyrrole-amidine" antibiotics,[4)] while the chemistry of β-aminopyrroles has little been studied apparently owing to the scanty of versatile synthetic procedure for the compounds.[5)] Only a few β-aminopyrroles have been prepared by a classical method involving nitration or nitrosation of appropriate α-substituted pyrroles followed by reduction.[6)] 3-Aminoindoles have

1) *a*) T. Murata, T. Sugawara, and K. Ukawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 2571 (1973); *b*) T. Murata and K. Ukawa, *ibid.*, **22**, 240 (1974); *c*) *Idem*, *ibid.*, **22**, 1212 (1974); *d*) This work was presented at the 7th Congress of Heterocyclic Chemistry (Japan), Chiba, Oct. 1974; Abstract Papers, p. 36.

2) Location: *17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan.*

3) A.I. Meyers and J.C. Sircar, "The Chemistry of the Cyano Group," Z. Rappoport ed., Interscience Publishers, London, 1970, p. 341.

4) M. Julia and N. Preau-Joseph, *C. R. Hebd. Seances Scand. Sci.*, **257**, 1115 (1963); S. Nakamura, H. Yonehara, and H. Umezawa, *J. Antibiotics, Ser. A*, **17**, 220 (1964); G.W. Probst, M.M. Hoehn, and B.L. Woods, *Antimicrobial Agents and Chemotherapy*, **1965**, 789; T. Takaishi, Y. Sugawara, and M. Suzuki, *Tetrahedron Lett.*, **1972**, 1873; F. Arcamone, P.G. Orezzi, W. Barbieri, V. Nicolella, and S. Penco, *Gazz. Chim. Ital.*, **96**, 1097 (1967).

5) P.S. Clezy, A.J. Liepa, and N.W. Weff, *Aust. J. Chem.*, **25**, 2687(1972); A.Z. Britten and G.W.G. Griffiths, *Chem. Ind.* (London), **1973**, 278; K.J. Morgan and D.P. Morrey, *Tetrahedron*, **22**, 57 (1966).

6) H Fischer and H. Orth, "Die Chemie des Pyrrols," 1, Akademische Verlag, Leipzig, 1934, p. 110; F. Yoneda, T. Miyake, and Y. Nitta, *Chem. Pharm. Bull.* (Tokyo), **15**, 8 (1967); D. Roileau, V. Daniel, E. Mosanu, and C.D. Nenitzescu, *Rev. Roum. Chim.*, **12**, 1367 (1967) [*C.A.*, **69**, 77043 (1968)]; J.B. Hester, Jr., *J. Org. Chem.*, **32**, 3804 (1967); J. Schmitt, C. Perrin, M. Langrois, and M. Suquet, *Bull. Soc. Chem. Fr.*, **1969**, 1227, 1234; J. Schmitt, M. Langrois, C. Perrin, and G. Gallet, *ibid.*, **1969**, 2004, 2008; G. Büchi and J.A. Raleigh, *J. Org. Chem.*, **36**, 873 (1971); A.P. Stoll and F. Troxler, *Helv. Chim. Acta*, **51**, 1864 (1968).

been in a situation similar to that of β-aminopyrroles.[7] A modification of Knorr's pyrrole synthesis recently reported by Zav'yalov *et al.*,[8] which involves heating of an acetylamino- or a benzoylaminoacetone derivative with barium hydroxide, gave β-acetamido- or β-benzoylaminopyrroles, respectively. Also of interest to us was the synthesis of 3-amino-2-benzoyl-1-ethoxycarbonylindole: Garcia *et al.* showed that N-ethoxycarbonylanthranitrile, on reaction with phenacyl bromide in the presence of sodium hydride, gave the corresponding 3-aminoindole derivative.[9]

The use of enaminonitrile for the synthesis of β-aminopyrroles and related heterocycles has received little attention except a short communication by Meyers *et al.*[3,10] who demonstrated that an enaminonitrile A spontaneously cyclized to a spiro system B; but the details have not been published (Chart 1). We found that electrophilic substitution of the methine of enamine C prepared from *tert*-butyl aminocyanoacetate and β-diketones or β-keto esters was followed by intramolecular cyclization to give 4-imino-2-pyrrolines D. Enamine C did not cyclize on treatment with sodium ethoxide; consequently, above reactions seemed to provide a new synthetic method for 3-aminopyrroles and related heterocycles.

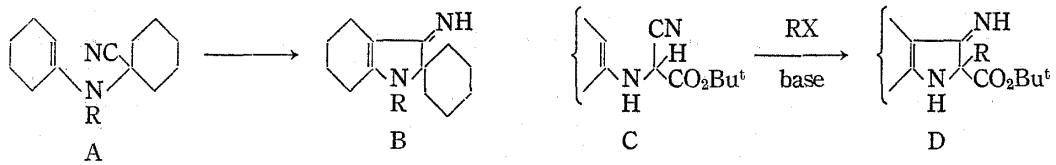


Chart 1

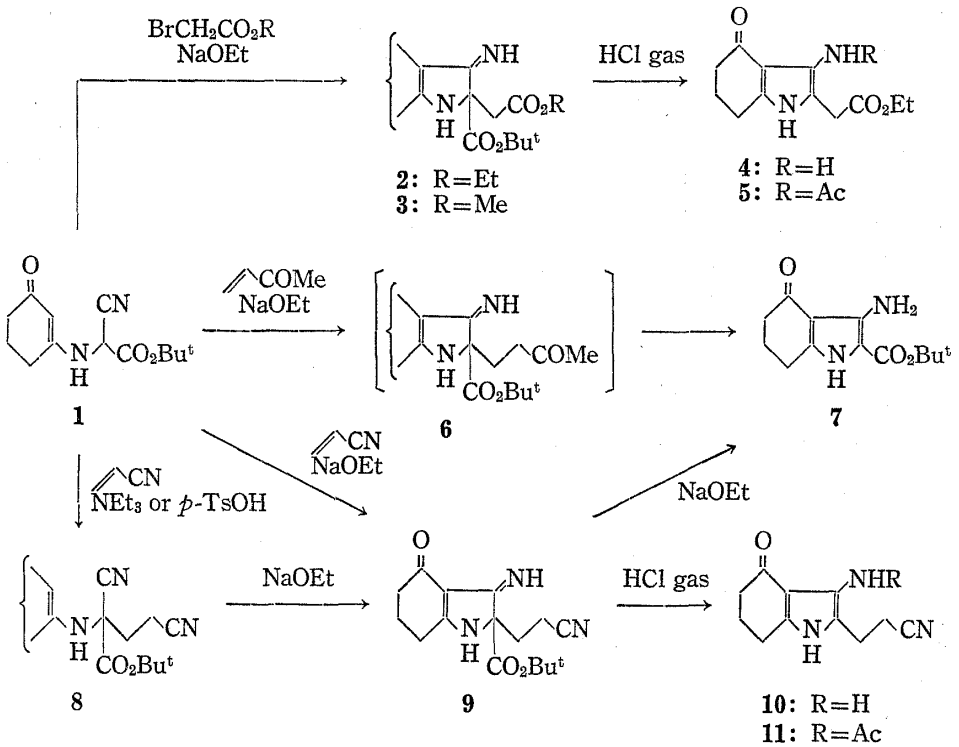
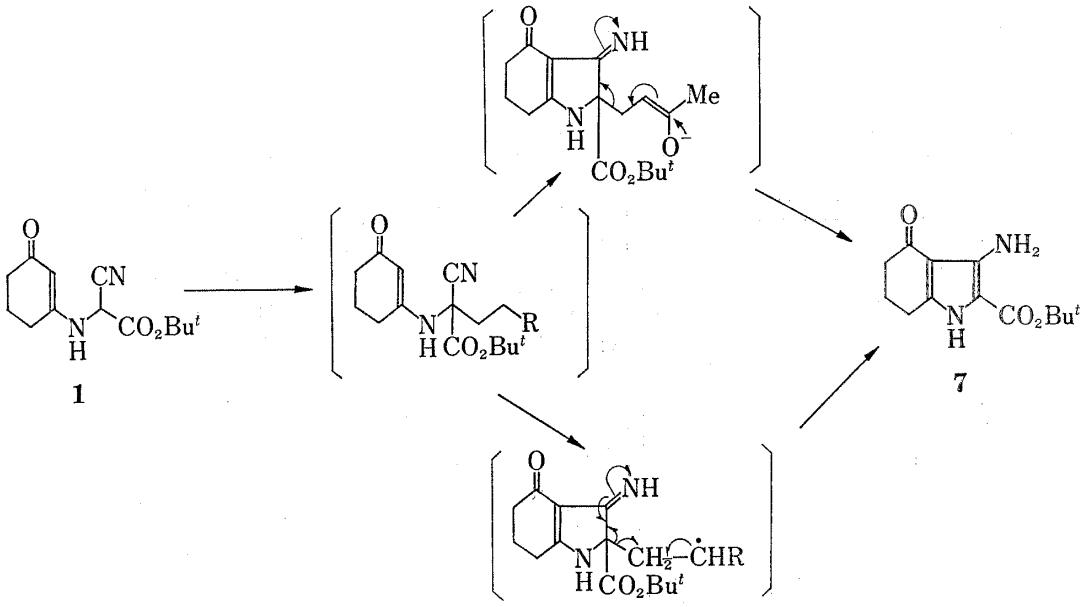


Chart 2

7) H. Hsonmin and F.G. Mann, *J. Chem. Soc.*, **1949**, 2903; R.G. Moore and P.J. Woitack, Jr., Brit. Pat. 816382 [*C. A.*, **55**, 188 (1961)].
8) S.I. Zav'yalov, N.I. Aronova, and I.F. Mustafaeva, *Izv. Aka. Nauk SSSR, Ser. Khim.*, **1973**, 1906 [*C. A.*, **80**, 36940 (1974)].
9) E.E. Garcia, L.E. Benjamin, and R.I. Fryer, *J. Heterocycl. Chem.*, **10**, 51 (1973).
10) A.I. Meyers, A. C. Kovelesky, and S. Singh, *Abstr. Papers Am. Chem. Soc.*, 155th Meeting, P (Org. Chem.), 49 (1968).

Synthesis of β-Aminopyrroles and Pyrido[3,2-*b*]indole Derivatives (Chart 2)

tert-Butyl 2-(3-oxo-1-cyclohexenylamino)cyanoacetate (**1**), readily prepared from cyclohexane-1,3-dione and *tert*-butyl aminocyanoacetate,[11] was treated with one equivalent of methyl or ethyl bromoacetate and two equivalents of the corresponding sodium alkoxide to give 2-*tert*-butoxycarbonyl-2-(2-ethoxycarbonylmethyl)-3-imino-4-oxo-4,5,6,7-tetrahydroindoline (**2**) or 2-*tert*-butoxycarbonyl-2-(2-ethoxycarbonylethyl)-3-imino-4-oxo-4,5,6,7-tetrahydroindoline (**3**), respectively in about 40% yields. Structures (**2** and **3**), assigned to them, received support from physicochemical measurements.[1a] Treatment of **2** with hydrogen chloride in chloroform generated 3-amino-2-ethoxycarbonylmethyl-4-oxo-4,5,6,7-tetrahydroindole (**4**); since the product was unstable even in a crystalline state, it was acetylated to the 3-acetamido derivative (**5**). Reaction of the enamine (**1**) with methyl vinyl ketone (MVK) in the presence of sodium ethoxide provided a good method for the synthesis of 3-amino-2-*tert*-butoxycarbonyl-4-oxo-4,5,6,7-tetrahydroindole (**7**). A small amount of **7** was also formed during the reaction of the enamine (**1**) with ethyl acrylate or acrylonitrile. The enamine (**1**) did not cyclize to **7** with sodium ethoxide. The reaction (1→7) can be accounted for by assuming that the cyclization took place *via* initial alkylation of the methine and that the initially introduced MVK moiety was eliminated from the iminopyrroline intermediate (**6**) (reverse Michael reaction, Chart 3).[12]



R=CO_2Et, CN, COMe

Chart 3

Reactions of **1** with acrylonitrile under various conditions provided evidence supporting the scheme suggested above. In the presence of triethylamine or *p*-toluenesulfonic acid, an initial substitution product, *tert*-butyl 2-(3-oxo-1-cyclohexenylamino)-2,4-dicyanobutyrate (**8**) was formed, while in the presence of sodium ethoxide in cold ethanol, 2-*tert*-butoxycarbonyl-2-(2-cyanoethyl)-3-imino-4-oxo-2,3,4,5,6,7-hexahydroindole (**9**) was formed. The reaction conducted with sodium ethoxide in hot ethanol afforded **7**. We also confirmed that **8** gave

11) This compound was prepared in a manner similar to that described for ethyl aminocyanoacetate. *Cf.* J.W. Cornforth, "The Chemistry of Penicillins," H.T. Clarke, J.R. Johnson, and R. Robinson ed., Princeton Univ. Press, Princeton, New Jersey, 1949, p. 725.

12) E.D. Bergmann, D. Ginsburg, and R. Pappo, "Organic Reactions," Vol. 10, R. Adams ed., John Wiley and Sons, Inc., London, 1959, p. 187.

9 on treatment with sodium ethoxide and that **9** yielded **7** on heating with sodium ethoxide. The 3-acetamido-2-(2-cyanoethyl)indole derivative (**11**) was prepared by treating **9** with aqueous hydrochloric acid followed by acetylation. The existence of an amino group in **7** was unequivocally demonstrated by the fact that **7** was diazotized to **15**[13] and that subsequent treatment of **15** with ethanol–sulfuric acid gave a deaminated pyrrole, 2-*tert*-butoxycarbonyl-4-oxo-4,5,6,7-tetrahydroindole (**16**) (Chart 4). Several derivatives of **7** (**12**, **13**, and **14**) were prepared. Acylation of **7** with acetyl chloride and the reaction with ethyl chloroformate gave products (**12** and **13**); on the other hand, treatment of **7** with ethyl bromoacetate–sodium carbonate yielded the 1-alkylated product, 3-amino-2-*tert*-butoxycarbonyl-2-ethoxycarbonylmethyl-4-oxo-4,5,6,7-tetrahydroindole (**14**). Compound **14** was converted to the 3-formylamino derivative, 1-ethoxycarbonylmethyl-3-formylamino-4-oxo-4,5,6,7-tetrahydroindole (**19**), on treatment with formic acid; the *tert*-butoxycarbonyl group at the 2-position was removed concomitantly.[14] 3-Aminotetrahydroindole (**7**) forms the hydrochloride salt, but the salt regenerated **7** on treatment with water, thus demonstrating the low basicity of the amino group.

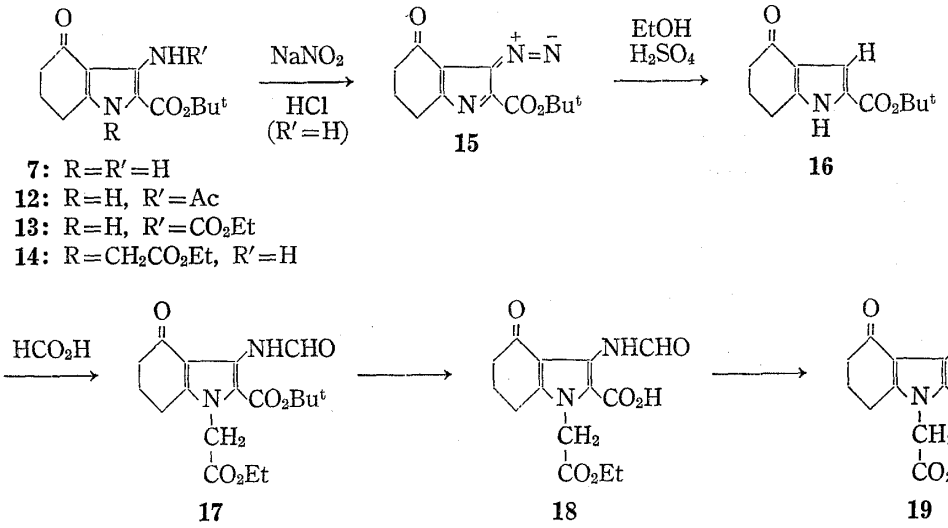
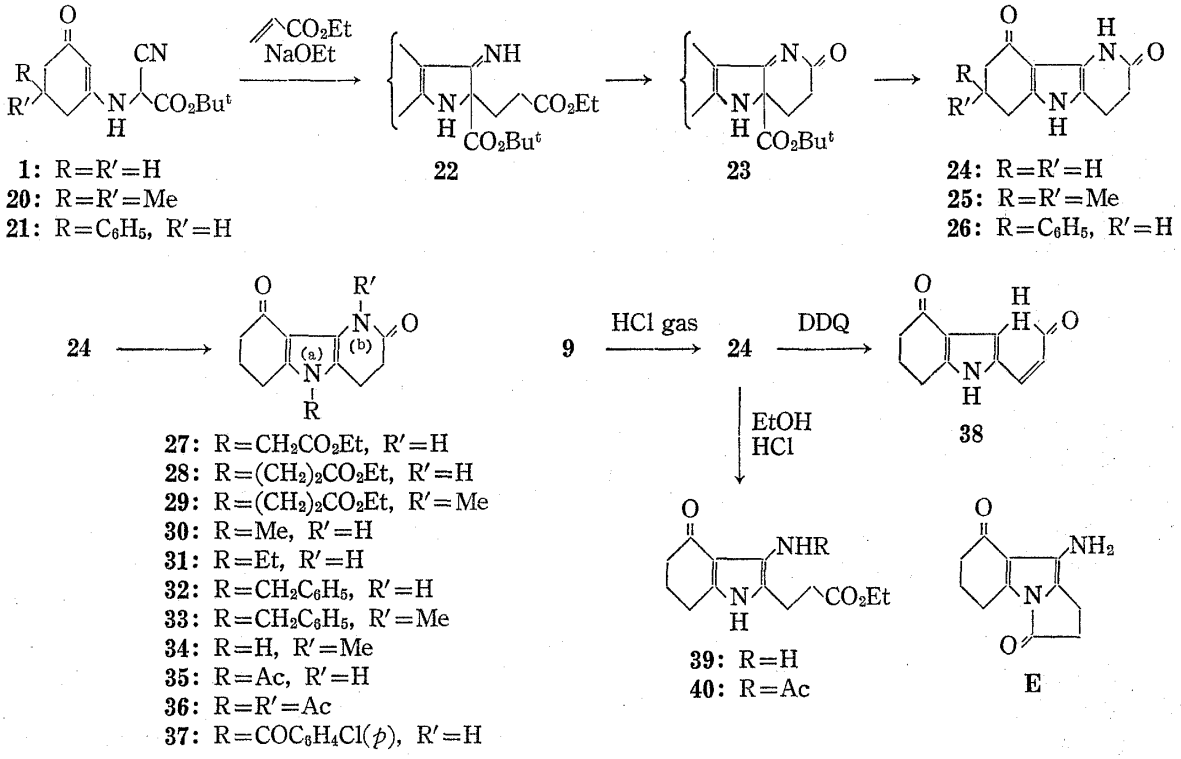


Chart 4

A modification of this process disclosed a synthetic route to new pyrido[3,2-*b*]indole derivatives (**24**, **25**, and **26**) as shown in Chart 5. The enamine (**1**), on treatment with ethyl acrylate and sodium ethoxide in warm ethanol, gave 2,9-dioxo-1,2,3,4,6,7,8,9-octahydro-5*H*-pyrido[3,2-*b*]indole (**24**) in about 40% yield. In this reaction, the intermediates (**22** and **23**) were also obtained in low yields. The nuclear magnetic resonance (NMR) spectrum [deuterated dimethyl sulfoxide (DMSO-d_6)] of **24** showed two singlets assignable to two NH protons at 8.06 and 11.06 ppm, respectively. The former could be assigned to the amide NH proton, while the latter to the pyrrolic NH proton. Several derivatives (**27**—**37**) of **24** were prepared. An N-substituted product (**27**), which shows one NH proton at 8.06 ppm in the NMR spectrum, was obtained by the reaction of **24** and ethyl bromoacetate in the presence of a catalytic amount of anhydrous potassium carbonate. Since alkylation should take place preferentially at the pyrrolic nitrogen $N_{(a)}$, which carries a proton more acidic than an amide proton, it is reasonable to conclude that the product (**27**) should be an $N_{(a)}$-alkylated derivative. Similarly, mono-N-methyl (**30**) and mono-N-benzyl derivative (**32**) are also assigned to $N_{(a)}$-alkylated

13) J.M. Tedder, "Advances in Heterocyclic Chemistry," Vol. 8, A.R. Katritzky and A.J. Boulton ed., Academic Press Inc., New York, 1967, p. 1.
14) K. Schofield, "Hetero-Aromatic Nitrogen Compounds—Pyrroles and Pyridines," Butterworths and Co., London, 1967, p. 94.

products. Another mono-N-methyl derivative (**34**), which was obtained by N-methylation of the $N_{(a)}$-benzyl derivative (**32**) followed by debenzylation, has physicochemical properties different from those of the $N_{(a)}$-methyl compound (**30**). In the NMR spectrum, the $N_{(b)}$-methyl compound (**34**) shows the pyrrolic NH proton at 10.18 ppm as a singlet. Therefore, the structure E for **24** was eliminated (Chart 5). $N_{(a)}$-Acylated products were also preferentially obtained in acylations of **24**; namely, compounds (**35** and **37**) were obtained by acetylation and *p*-chloro-



1: R=R′=H
20: R=R′=Me
21: R=C_6H_5, R′=H

22

23

24: R=R′=H
25: R=R′=Me
26: R=C_6H_5, R′=H

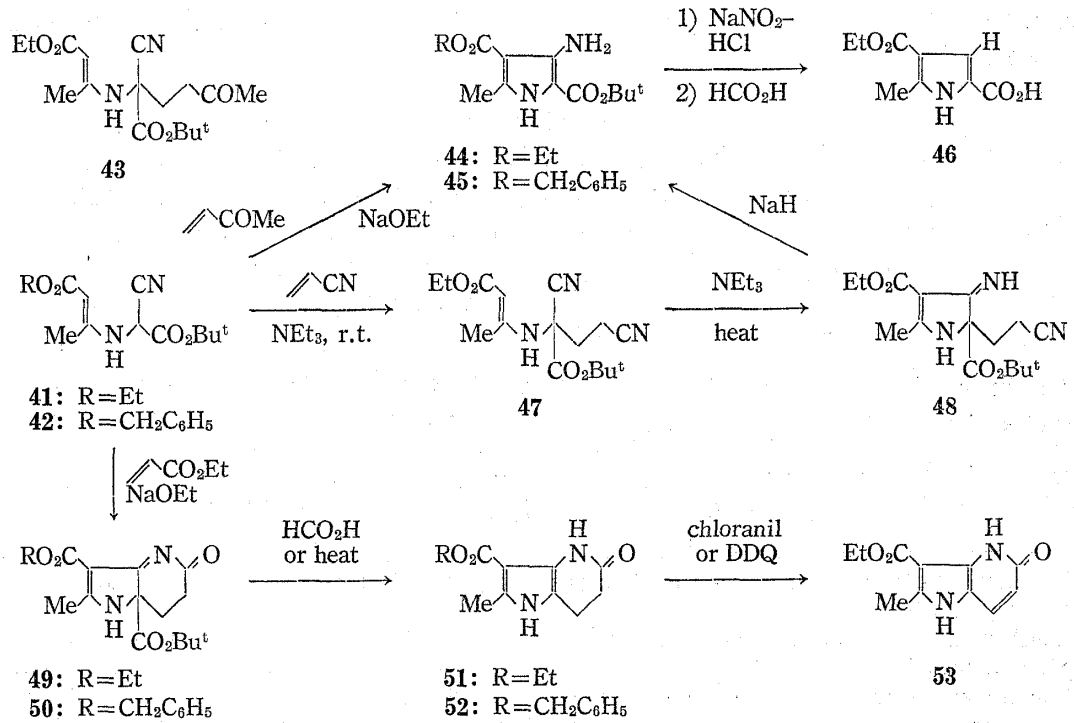
27: R=CH_2CO_2Et, R′=H
28: R=$(CH_2)_2CO_2Et$, R′=H
29: R=$(CH_2)_2CO_2Et$, R′=Me
30: R=Me, R′=H
31: R=Et, R′=H
32: R=$CH_2C_6H_5$, R′=H
33: R=$CH_2C_6H_5$, R′=Me
34: R=H, R′=Me
35: R=Ac, R′=H
36: R=R′=Ac
37: R=$COC_6H_4Cl(p)$, R′=H

38

39: R=H
40: R=Ac

E

Chart 5



43

44: R=Et
45: R=$CH_2C_6H_5$

46

41: R=Et
42: R=$CH_2C_6H_5$

47

48

49: R=Et
50: R=$CH_2C_6H_5$

51: R=Et
52: R=$CH_2C_6H_5$

53

Chart 6

benzoylation, respectively. The dehydrogenation of **24** was effected with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as shown in Chart 5. Alcoholysis of **24** with ethanolic hydrochloric acid at room temperature afforded 3-amino-2-(2-ethoxycarbonylethyl)-4-oxo-4,5,6,7-tetrahydroindole (**39**), which was acetylated to the acetamido derivative (**40**).

3-Aminopyrroles and Pyrrolo[3,2-*b*]pyridines[15] (Chart 6)

The above intramolecular reactions were then applied to the enaminonitriles (**41** and **42**) readily obtained by condensation of appropriate acetoacetates with *tert*-butyl aminocyanoacetate. Thus, a new 3-amino-2-*tert*-butoxycarbonyl-4-ethoxycarbonyl-5-methylpyrrole (**44**) has been prepared in over 90% yields by the reaction of the enamine (**41**) with MVK in the presence of sodium ethoxide. The product (**44**) has been correlated with authentic 2-carboxy-4-ethoxycarbonyl-5-methylpyrrole (**46**)[16] by deamination and subsequent removal of the *tert*-butyl group with formic acid. Similar reactions (**41**→**47**→**48**→**44**) have been achieved with acrylonitrile. In the case of MVK, the initial substitution product (**43**) could not be isolated (Chart 6).

The reaction of the enamines (**41** and **42**)[17] with ethyl acrylate provided a route to new pyrrolo[3,2-*b*]pyridine derivatives (**51** and **52**). The enamines (**41** and **42**) reacted with ethyl acrylate-sodium ethoxide in cold ethanol to afford 7a-*tert*-butoxycarbonyl-3-ethoxycarbonyl-2-methyl-5-oxo-5,6,7,7a-tetrahydro-1*H*-pyrido[3,2-*b*]pyridine (**49**) and 3-benzyloxycarbonyl-7a-*tert*-butoxycarbonyl-2-methyl-5-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine (**50**), respectively. The products were then transformed into ethyl and benzyl 2-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine 3-carboxylates (**51** and **52**), respectively by thermolysis. The conversions (**49**→**51** and **50**→**52**) were also readily accomplished by an acid such as formic acid or trifluoroacetic acid. Dehydrogenation of the tetrahydropyrrolopyridine (**51**) was effected with chloranil or DDQ to obtain the pyridone, 3-ethoxycarbonyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine (**53**). The α-pyridone structure for **53** was based on spectral evidence. The NMR spectrum of **53** clearly shows two one-proton doublets (J=10 Hz) at 6.08 and 7.57 ppm due to the double bond; the infrared (IR) spectrum (Nujol) of **51** shows bands at 1690 (ester) and 1645 cm^{-1} (amide), the latter shifted to 1620 cm^{-1} in **53**. Compound **49** gave a mixture of the 3-aminopyrrole (**44**) and the pyrrolopyridine (**51**) on heating with sodium ethoxide. This fact can be explained by considering an intermediate **F** as shown in Chart 7.

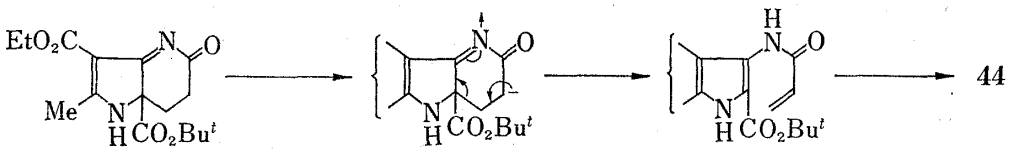


Chart 7

Participation of the Adjacent Ester Group in the Intramolecular Reactions—Formation of Pyrrolines and 3-Hydroxypyrrole (Chart 8)

Attention was then turned to the course of the intramolecular reactions. It seems reasonable to consider that the bulky *tert*-butyl group in the intermediate G would inhibit

15) R.E. Willete, "Advances in Heterocyclic Chemistry," Vol. 9, A.R. Katritzky and A.J. Boulton ed., Academic Press, New York, 1968, p. 27.
16) H. Fischer and M. Hussong, *Ann. Chem.*, **492**, 128 (1932); H. Shinohara, H. Sugimoto, and E. Imoto, *Nippon Kagaku Zasshi*, **83**, 612 (1962).
17) In Charts 6 and 9, the enamines (**41** and **42**) are expediently pictured as *trans*; however, we have noticed the isomerization in the compounds. *Cf.* S.K. Malhotra, "Enamines; Synthesis, Structure and Reactions," A.G. Cook ed., Marcel Dekker, Inc., New York, 1969, p. 35.

the course of the intramolecular reaction to give H, and consequently accelerate another intramolecular reaction, attack of the enamine on the cyano group, to yield D. In order to clarify the problem, we have examined the reactions of the enaminonitriles (**54**—**56**) carrying an ethoxy instead of the butoxy group in **41**. The reaction of ethyl ester of the enamine (**54**) with vinyl compounds gave the pyrrolinones (**58**—**60**), products due to the intramolecular reaction of the enamine with the ester carbonyl group (path b). Now, the products (**44**, **48**, **49**, and **51**) due to the reaction in which the cyano group had participated, were not observed. On the other hand, compounds (**58**—**60**) were not detected in the reaction of the enamine (**41**). Thus, two kinds of intramolecular reactions have been demonstrated with intermediate (**57**): one applies to the nitriles (path a) while the other to the esters (path b). A bulky *tert*-butyl group prevents the latter reaction. Similar intramolecular reactions have been observed in the reactions of ester enamines having a secondary methyl group (**55** and **56**) (Chart 9).

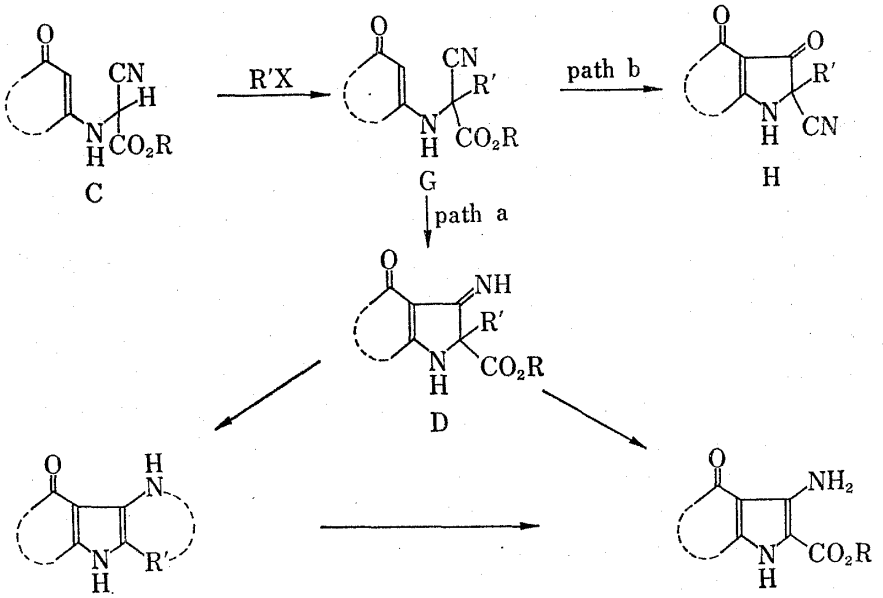


Chart 8

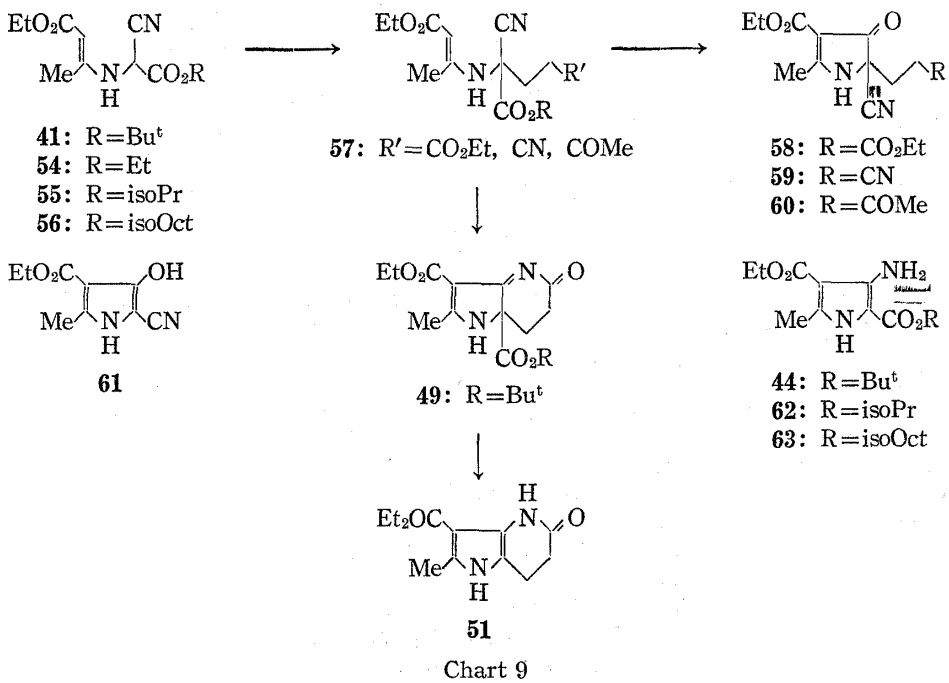


Chart 9

Thus, the enamines (**55** and **56**) on treatment with ethyl acrylate gave a mixture of the pyrrolopyridine (**49**) and a pyrrolinone, 5-cyano-3-ethoxycarbonyl-5-(2-ethoxycarbonylethyl)-2-methyl-4-oxo-2-pyrroline (**58**). No ester exchange reaction of **55** and **56** has occurred under the reaction conditions. Reactions of the enamines (**55** and **56**) with MVK in the presence of sodium ethoxide yielded the corresponding 2-alkoxycarbonyl-3-amino-4-ethoxycarbonyl-5-methylpyrroles (**62** and **63**). The enamine (**54**) reacted with acrylonitrile in the presence of sodium methylsulfinyl methide (dimsyl sodium) at room temperature to give the 2-cyano-4-ethoxycarbonyl-3-hydroxy-5-methylpyrrole (**61**) in 64% yield.[18] This reactions (**54**→**61**) contrast with the reaction where the 3-aminopyrroles (**44**) was obtained upon treating enamine (**41**) with MVK-sodium ethoxide (Chart 6).

The structure (**58a** or **58b**) is assignable to the pyrrolinone (**58**) (Chart 10). Since the ultraviolet (UV) spectrum of **58** in ethanol is extremely similar to that of a known pyrrolinone (**64**),[19] **58a** must be a principal component in ethanol. But the color reaction of enolic hydroxy group with ferric chloride is faintly positive; consequently, **58** will partly exist as a hydroxypyrrolenine structure (**58b**). The pyrrolinone (**58**) was innert to the Reformatsky and the Wittig reactions, but gave the O-acetylpyrrolenine, 3-acetoxy-2-cyano-4-ethoxycarbonyl-2-(2-ethoxycarbonylethyl)-5-methyl-2*H*-pyrrole (**65**) on acetylation with acetic anhydride-sodium acetate. Methylation of **58** with methyl iodide-potassium carbonate afforded a product to which we allotted the N-methyl-(**66**) or O-methyl structure (**67**). The pyrrolinone (**58**) was converted into the monocarboxylic acid, 5-(2-carboxyethyl)-5-cyano-3-ethoxycarbonyl-2-methyl-4-oxo-2-pyrroline (**68**); and the latter was derived into the lactone, 7a-cyano-3-ethoxycarbonyl-2-methyl-5-oxo-5,6,7,7a-tetrahydropyrano[3,2-*b*]pyrrole (**69**) by the use of dicyclohexylcarbodiimide (DCC). The lactone (**69**) readily regenerated the starting pyrrolinone (**58**) on treatment with ethanolic hydrochloric acid. Since the UV spectrum of the lactone (**69**) was similar to that of the acetate (**65**), we assumed that **65** had an O-acetyl structure carrying a pyrrolenine system.

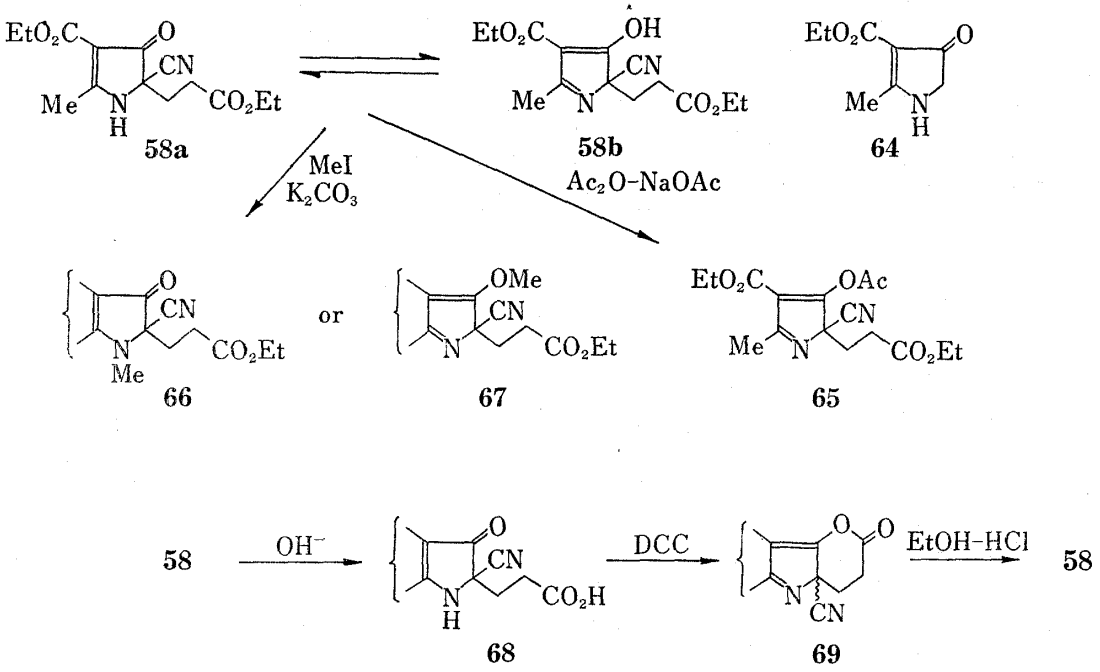


Chart 10

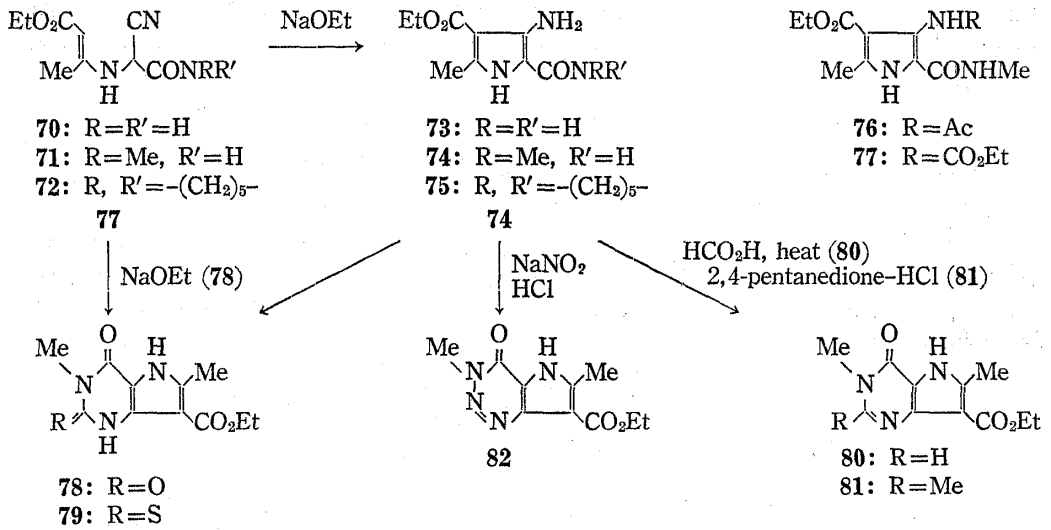
18) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, 1967, p. 310. The pyrrolinone (**59**) also afforded the pyrrole (**61**) on treatment with dimsyl sodium; compound **61** gave **59** on treatment with acrylonitrile–sodium ethoxide.

19) E. Benary and B. Silbermann, *Chem. Ber.*, **46**, 1363 (1913); J. Davoll, *J. Chem. Soc.*, **1953**, 3802.

Synthesis of New 3-Amino-2-carbamoylpyrroles—A New Route to Pyrrolo[3,2-*d*]pyrimidines (Chart 11)

As a logical extention of our studies on the intramolecular reactions of certain enaminonitriles, we have investigated with the enaminonitriles (**70**—**72**) carrying a carbamoyl group in the molecules; **70**—**72** were prepared by condensing ethyl acetoacetate with aminocyanoacetamides.[20] Attempts were made to obtain the new 3-amino-2-carbamoylpyrroles (**73**—**75**) by the use of enamine addition to nitrile and to further convert such an appropriate product as 3-amino-4-ethoxycarbonyl-5-methyl-2-methylcarbamoylpyrrole (**74**) into several pyrrolo[3,2-*d*]pyrimidines. This conversion is also of interest because there has been no report of pyrrolo[3,2-*d*]pyrimidine synthesis starting from 3-aminopyrroles;[21] this is undoubtedly due to the absence of good preparative method for suitable 3-aminopyrroles. We have successfully synthesized new aminocarbamoylpyrroles (**73**—**75**) and pyrrolo[3,2-*d*]pyrimidines (**78**—**81**).[1b] In addition, a new pyrrolo[3,2-*d*]-*v*-triazine (**82**) has been prepared.

The enamines (**70**—**72**) were treated with sodium ethoxide in ethanol to cyclize to the expected products (**73**—**75**), respectively. Though the yield of **73** was rather poor (30%), the latter two compounds (**74** and **75**) were obtained in about 75% yields. There was no need for the substitution at the methine of the enamines (**70**—**72**) with electrophile such as acrylic acid derivatives and MVK. The structure of new aminocarbamoylpyrroles (**73**—**75**) have been established on the basis of physicochemical data; particularly, the NMR spectra (dimethyl sulfoxide (DMSO)-d_6) of the compounds provided an unequivocal proof showing the 3-amino and pyrrolic NH protons near 5 and 11 ppm, respectively. As would be expected, N-methylcarbamoylpyrrole (**74**) was easily transformed into new pyrrolo[3,2-*d*]pyrimidines by the following reactions. Ethyl chloroformate-pyridine reacted with **74** to yield the urethane, 4-ethoxycarbamoyl-3-ethoxycarbonylamino-5-methyl-2-methylcarbamoylpyrrole (**77**); the latter on treatment with sodium ethoxide cyclized quantitatively to the 2,4-dioxo derivative, 7-ethoxycarbonyl-3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1*H*,5*H*-pyrrolo[3,2-*d*]-pyrimidine (**78**). The 2-thione compound (**79**) was readily prepared by the reaction of **74**



70: R=R′=H
71: R=Me, R′=H
72: R, R′=-(CH$_2$)$_5$-
73: R=R′=H
74: R=Me, R′=H
75: R, R′=-(CH$_2$)$_5$-
76: R=Ac
77: R=CO$_2$Et
78: R=O
79: R=S
80: R=H
81: R=Me
82

Chart 11

20) The aminocyanoacetamides were prepared by reduction of the corresponding oximinocyanoacetamides. *Cf.* L.H. Smith, Jr. and P. Yates, *J. Am. Chem. Soc.*, **76**, 6080 (1954); O. Touster, "Organic Reactions," Vol. 7, R. Adams ed., John Wiley and Sons, Inc., New York, 1953, p. 327.

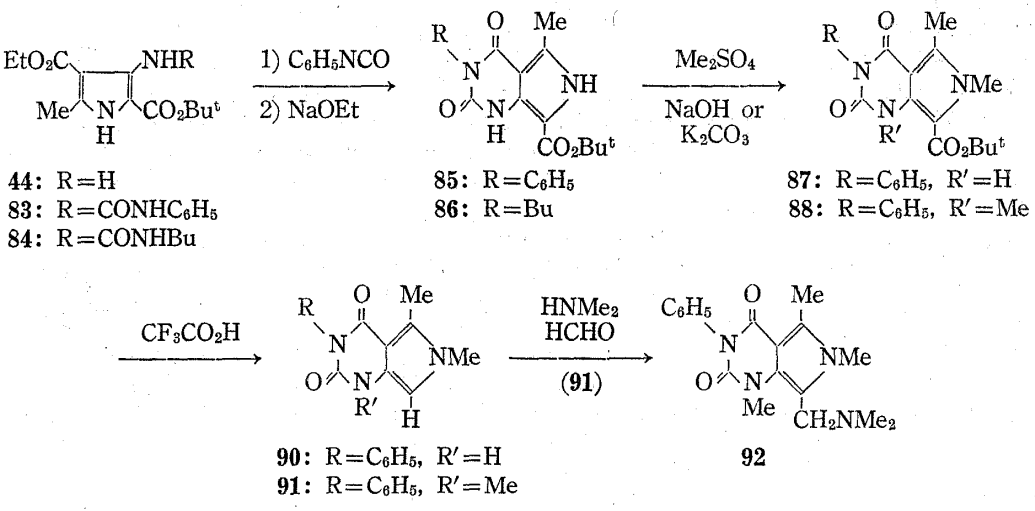
21) The pyrrolo[3,2-*d*]pyrimidines have been prepared from pyrimidine derivatives carrying an active methyl group in the molecules; recently, a thermal conversion of several pyrimido[4,5-*b*]-1,4-thiazines into pyrrolo[3,2-*d*]pyrimidines was reported. See K. Tanaka, T. Sugawa, R. Nakamori, Y. Sanno, Y. Ando, and K. Imai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1024 (1964); H. Fenner and H. Motschall, *Tetrahedron Lett.*, **1971**, 4185.

with potassium xanthogenate in pyridine and subsequent treatmnnt with aqueous acetic acid. The thioamide structure of **79** was based on the presence of IR bands ascribable to a C=S bond at 3360, 1580, and 1310 cm^{-1}.[22] Heating of **74** with formic acid gave the 4-oxo-3,4-dihydropyrrolo[3,2-*d*]pyrimidine (**80**) in 90% yield. Support for the structure (**80**) comes from its NMR spectrum (CF_3CO_2D) which shows the C_2-proton at 9.27 ppm as a sharp singlet. The corresponding 2-methyl compound (**81**) was prepared by acetylation of **74** with acetic anhydride-sodium acetate followed by treatment with sodium ethoxide-induced cyclization of the resulting acetate (**76**). Compound **81** could also be prepared by the reaction of **74** with 2,4-pentanedione in ethanolic hydrochloric acid. Treatment of the methylcarbamoylpyrrole (**74**) with sodium nitrite in aqueous hydrochloric acid afforded the pyrrolotriazine (**82**).

A New Route to 2,4-Dioxopyrrolo[3,4-*d*]pyrimidines (Chart 12)

It is reasonable to predict that the 3-aminopyrrole (**44**) can be converted to several 2,4-dioxopyrrolo[3,4-*d*]pyrimidines containing a genuine pyrrole nucleus in the molecules *via* ureas such as **83** and **84**, a conventional route, because **44** has a structural feature suitable for the purpose. Since such dioxopyrrolo[3,4-*d*]pyrimidines have never been prepared, they drew our attention by virtue of the structure relationships to 7- and 9-deazapurines. Further, there has been no report of the use of 3-aminopyrroles for pyrrolo[3,4-*d*]pyrimidine synthesis;[23] this is presumably due to the absence of good preparative method for 3-aminopyrroles.

The 3-aminopyrrole (**44**) was heated in acetonitrile with phenyl or butyl isocyanate to obtain the urea (**83** or **84**), respectively. On treatment with sodium ethoxide, **83** and **84** underwent smooth cyclizations to give the expected products (**85** and **86**) in high yields. N-methylation of **85** with dimethyl sulfate-sodium hydroxide in aqueous methanol, or with dimethyl sulfate-potassium carbonate in DMSO yielded the di-N-methyl compound (**88**). The mono-N-methyl compound (**87**) was also isolated in these reactions.[1c] Stepwise reactions (**85**→**87**; **87**→**88**) using the latter reagent-solvent system gave satisfactory results. Methylation of the pyrrole (**44**) with methyl iodide-potassium carbonate in DMSO gave a mono-N-methyl pyrrole, 3-amino-2-*tert*-butoxycarbonyl-4-ethoxycarbonyl-1,5-dimethylpyrrole (**89**) in which the pyrrolic nitrogen had been alkylated; the product **89** was transformed into **87** in the same manner as the reaction (**44**→**85**). The mono-N-methyl (**87**) and di-N-methyl



44: R=H
83: R=CONHC$_6$H$_5$
84: R=CONHBu

85: R=C$_6$H$_5$
86: R=Bu

87: R=C$_6$H$_5$, R′=H
88: R=C$_6$H$_5$, R′=Me

90: R=C$_6$H$_5$, R′=H
91: R=C$_6$H$_5$, R′=Me

92

Chart 12

22) W. Walter and J. Voss, "Chemistry of Amide," J. Zabicky ed., Interscience Publishers, London, 1970, p. 395.

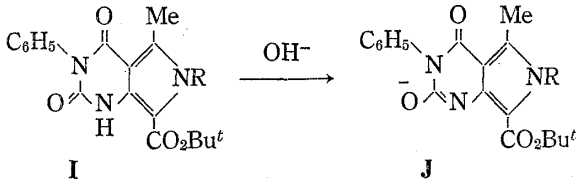
23) For the known pyrrolo[3,4-*d*]pyrimidine syntheses, see P.L. Southwick, R. Madhav, and J.A. Fitzgerald, *J. Heterocycl. Chem.*, **6**, 507 (1969) and the literature cited therein; B. Hansen and H. von Dobeneck, *Chem. Ber.*, **105**, 3630 (1972).

compound (**88**) were treated with trifluoroacetic acid to yield 5,6-dimethyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-6*H*-pyrrolo[3,4-*d*]pyrimidine (**90**) and 1,5,6-trimethyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-6*H*-pyrrolo[3,4-*d*]pyrimidine (**91**), respectively. A Mannich reaction of the latter (**91**) with dimethylamine and formaldehyde afforded **92**. The UV spectra of the dioxopyrrolopyrimidines (**83**, **87** and **88**) are given in Table I. A bathochromic shift of *ca.* 25 nm ovserved on addition of an alkali is presumably due to the formation of an anion **J** from the neutral molecule **I**.[24]

Table I. UV Maxima of **85**, **87**, **88**, and Related Compounds (**44** and **83**)

Compound	λ_{max} nm(ε) In EtOH	+aq. NaOH[a]
85	240 (38000), 271.5 (19000)	248, 302
87	242.5 (42200), 273 (18100)	245, 302
88	243 (33200), 250 (12700)	243, 281
44	236.5 (34300), 280 (13600)	
83	242 (34600), 277 (15400)	

a)



I R=H or Me **J**

Experimental

All melting points were taken with a Yanagimoto's microscope hot stage and are uncorrected. NMR spectra were obtained using a Varian T-60, A-60 or with HA-100 instrument. Chemical shifts are reported in ppm downfield from internal tetramethylsilane (TMS) (δ) and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. IR spectra were measured on a Perkin-Elmer 450 spectrophotometer and mass spectra (MS) were obtained with a Hitachi RMS-4 or RMU-6D instrument. For silica gel chromatography, Kieselgel G (0.05—0.2 mm, Merck) was used; for alumina chromatography, neutral alumina (Woelm, activity I) was used unless otherwise noted.

General Procedure for the Preparation of the Starting Enaminonitriles; *tert*-Butyl 2-(3-oxo-1-cyclohexenylamino)cyanoacetate (1)——Cyclohexane-1,3-dione (21 g), *tert*-butyl α-aminocyanoacetate (33 g), anhyd. Na_2SO_4 (100 g) and a catalytic amount of *p*-TsOH in benzene (600 ml) were heated at 70° overnight. After cooling, the reaction mixture was treated with aq. 2 N Na_2CO_3 solution and the aq. phase was acidified with dil. HCl to pH 3. The enamine **1** precipitated as a yellow viscous oil; the supernatant was decanted and the oil was dissolved in AcOEt. After removal of the AcOEt, **1** (yield 40 g, 86%) was recrystallized from AcOEt–hexane to obtain pale yellow needles, mp 117—118°. *Anal.* Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.09; H, 7.30; N, 11.08. UV λ_{max}^{EtOH} nm (ε): 276 (24800). IR ν_{max}^{KBr} cm^{-1}: 3400, 3250, 1740, 1610, 1585. NMR ($CDCl_3$): 1.52 (9H, s), 2.0 (2H, q), 2.4 (4H, quintet), 4.71 (1H, d, J=7 Hz), 5.11 (1H, s), 6.17 (1H, d, J=7 Hz). Other enaminonitriles (**20**, **21**, **41**, **42**, **54**, **55**, **56**, **70**, **71** and **72**) were prepared in the same manner as above and their melting points and analytical data are given in the following. **20**, amorphous, MS *m/e* 278 (M^+). **21**, oil, MS *m/e* 326 (M^+). **41**, colorless plates of mp 135—136° (ether). *Anal.* Calcd. for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 57.99; H, 7.30; N, 10.59. **42**, colorless plated of mp 74—75° (ether–hexane). *Anal.* Calcd. for $C_{18}H_{22}N_2O_4$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.74; H, 7.00; N, 11.09. **54**, colorless plates of mp 85—86° (ether). *Anal.* Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.27; H, 6.58; N, 11.39. **55**, colorless plates of mp 74—75° (ether–hexane), *Anal.* Calcd. for $C_{12}H_{18}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.56; H, 6.78; N, 8.57. **56**, oil, MS *m/e* 324 (M^+). **70**, colorless plates of mp 145° (sintered at 135°, ether–hexane), *Anal.* Calcd. for $C_9H_{13}N_3O_3$: C, 51.17; H, 6.20; N, 19.90. Found: C, 51.08; H, 6.10; N, 19.77. **71**, colorless plates of mp 119—120° (ether). *Anal.* Calcd.

24) G. Nübel and W. Pfleiderer, *Chem. Ber.*, **98**, 1060 (1965).

for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.47; H, 6.68; N, 18.38. **72**, colorless plates of mp 121—123° (AcOEt–hexane), *Anal.* Calcd. for $C_{14}H_{23}N_3O_3$: C, 60.19; H, 7.58; N, 15.04; Found: C, 59.88; H, 7.61; N, 15.02.

2-*tert*-Butoxycarbonyl-2-(2-ethoxycarbonylmethyl)-3-imino-4-oxo-4,5,6,7-tetrahydroindoline (2)——Ethyl bromoacetate (7.0 g) was added at 0° to a stirred mixture of **1** (10 g) and NaOEt (prepared from 2.0 g of sodium) in ethanol (18 ml). The reaction mixture was heated at 70° for 30 min and concentrated. The residue was partitioned between water and AcOEt, and the organic layer was washed with a saturated aqueous NaCl solution and then extracted with 2 N HCl. After neutralization of the aq. phase with aq. NaOH, the product **2** was again extracted with CH_2Cl_2. Evaporation of the solvent left a viscous oil, which was crystallized from AcOEt–hexane to obtain colorless plates of **2**, mp 131—132°; yield 5.4 g, 40%. *Anal.* Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.41; H, 7.48; N, 8.17. MS *m/e*: 336 (M^+), 235, 234, 189, 163, 149, 57 (base peak). UV λ_{max}^{EtOH} nm (ε): 260 (9150), 317 (7500). IR ν_{max}^{KBr} cm^{-1}: 3350, 3050, 1735, 1660, 1620, 1575. NMR ($CDCl_3$): 2.40 (1H, d, J=18 Hz), 3.50 (1H, d, J=18 Hz).

2-*tert*-Butoxycarbonyl-2-(2-ethoxycarbonylethyl)-3-imino-4-oxo-4,5,6,7-tetrahydroindoline (3)——Compound **3** was prepared in the same manner as described above; yield 40%. Recrystallization from AcOEt–hexane gave colorless plates, mp 157—158°. MS *m/e*: 322 (M^+), 221, 189, 179, 163, 147, 121, 57 (base peak). IR ν_{max}^{KBr} cm^{-1}: 3450, 3300, 1730, 1645, 1590, 1530. NMR ($CDCl_3$): 1.45 (9H, s), 2.20 (2H, q), 2.4—2.5 (5H, m), 3.49 (1H, d), 3.74 (3H, s), 7.54 (1H, broad s), 8.07 (1H, broad s).

3-Amino-2-ethoxycarbonylmethyl-4-oxo-4,5,6,7-tetrahydroindole (4) and 3-Acetamido Derivative (5)——Dry HCl gas was bubbled through a solution of **2** (12 g) in CH_3NO_2 (70 ml) for 30 min. After standing at room temperature for 40 min, the solvent was removed *in vacuo*. The residue was diluted with water (60 ml) and extracted with ether (50 ml×2). The aq. phase was neutralized with 2 N Na_2CO_3 to precipitate **4**, which was dissolved in CH_2Cl_2. Evaporation of the solvent left crystalline product **4** (8.7 g).

A solution of **4** (6.2 g) in CH_2Cl_2 (35 ml)–tetrahydrofuran (THF) (35 ml) was treated with NEt_3 (1.9 ml) and AcCl (1.5 ml). After working up in the usual way, 3-acetamido derivative (**5**) (7.0 g) was obtained. Recrystallization from benzene–acetone gave colorless plates of **5**, mp 177—178°. *Anal.* Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.60; H, 6.53; N, 9.87. MS *m/e*: 278 (M^+), 235, 190, 163 (base peak). UV λ_{max}^{EtOH} nm (ε): 245 (9800), 280 (shoulder, 5500). IR ν_{max}^{KBr} cm^{-1}: 3350—2700, 1750, 1660, 1640, 1620 (shoulder), 1565, 1525. NMR (DMSO-d_6): 1.18 (3H, t), 1.94 (3H, s), 2.27 (2H, t), 2.70 (2H, t), 3.54 (2H, s), 4.05 (2H, q), 8.88 (1H, s), 11.09 (1H, s).

3-Amino-2-*tert*-butoxycarbonyl-4-oxo-4,5,6,7-tetrahydroindole (7)——a) Methyl acrylate (700 ml) was added at 0° to a mixture of **1** (1.8 g) and NaOEt (prepared from 300 mg of sodium) in ethanol (20 ml). After stirring at room temperature for 1 hr, the mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with AcOEt. The organic layer was washed with water and dried (anhydrous Na_2SO_4). Evaporation of the AcOEt left yellow crystals (1.1 g, 61%), which were recrystallized from benzene–hexane to obtain pale yellow plates of **7** (0.8 g). An analytical sample was obtained by recrystallization from aq. dioxane; mp 215—220° (flocculated at 130°). *Anal.* Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.34; H, 7.41; N, 11.01. MS *m/e*: 250 (M^+), 195, 194 (base peak), 177, 176, 148. UV λ_{max}^{EtOH} nm (ε): 254.5 (29900), 283 (11500). IR ν_{max}^{KBr} cm^{-1}: 3515, 3390, 3255, 1680, 1635, 1595. NMR (DMSO-d_6): 1.50 (9H, s), 1.98 (2H, broad q), 2.28 (2H, broad t), 2.65 (2H, t), 5.50 (2H, broad s), 11.00 (1H, broad s).

b) A mixture of **1** (1.8 g), MVK (700 mg) and NaOEt (prepared from 300 mg of sodium and 20 ml of ethanol) was stirred for 1 hr at room temperature. The mixture was diluted with water and extracted with AcOEt. The AcOEt extract was washed with water, dried and evaporated to leave crystalline **7** (1.1 g, 44%). Recrystallization from benzene–hexane gave 800 mg of the pure product.

c) A mixture of **7** (100 mg), acetone (10 ml) and conc. HCl (0.2 ml) was heated at 45° for 30 min. After cooling, the crystals were collected and washed with acetone to obtain the hydrochloride of **7** (80 mg) as pale yellow fine plates, mp *ca.* 220°. IR ν_{max}^{KBr} cm^{-1}: 3255, 3000—2500, 1730, 1675, 1610, 1510.

***tert*-Butyl-2-(3-oxo-1-cyclohexenylamino)-2,4-dicyanobutyrate (8)**——A mixture of **1** (500 mg), acrylonitrile (0.2 ml), NEt_3 (0.2 ml) and *tert*-BuOH (10 ml) was allowed to stand at room temperature for 3 days. The solvent was evaporated and the residual crystals were washed with chilled benzene to obtain 600 mg of **8** (99%). An analytical sample, colorless plates, mp 151—153°, was obtained by recrystallization from benzene. *Anal.* Calcd. for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.24; H, 6.95; N, 13.87. The use of *p*-TsOH in place of NEt_3 also afforded **8** in a similar yield. Treatment of **8** with NaOEt in cold ethanol gave **9**, identified with the one obtained below by IR spectral comparison.

2-*tert*-Butoxycarbonyl-2-(2-cyanoethyl)-3-imino-4-oxo-2,3,4,5,6,7-hexahydroindole (9)——a) Acrylonitrile (1.1 g) was added dropwise at 0° to a mixture of **1** (5 g) and NaOEt (2 mol equivalents) in ethanol (55 ml). The reaction mixture was stirred at room temperature for 45 min, diluted with aq. HCl at 0° and concentrated *in vacuo*. The residue was extracted with AcOEt; evaporation of the AcOEt extract left crude **9** (3.5 g, 58%). Recrystallization from $CHCl_3$–hexane gave colorless needles, mp 175—177°. *Anal.* Calcd. for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.29; H, 6.97; N, 13.71. MS *m/e*: 303 (M^+), 203, 163, 57 (base peak). UV λ_{max}^{EtOH} nm (ε): 258 (10400), 317 (7450).

b) The mother liquor of **9** above was chromatographed on silica gel; elution with $CHCl_3$–ethanol (15: 1) gave **7** (500 mg).

c) A solution of **9** (300 mg) in ethanol (20 ml) was mixed with NaOEt (prepared from 50 mg of sodium) in ethanol (10 ml), and the mixture was heated at 60° for 4 hr. After evaporation of the solvent, the residue was extracted with AcOEt. The product was chromatographed on silica gel (20 g). Elution with $CHCl_3$–ethanol (15: 1) afforded **7** (63 mg).

3-Amino-2-(2-cyanoethyl)-4-oxo-4,5,6,7-tetrahydroindole (10) and 3-Acetamido Derivative (11)——A solution of **9** (2.3 g) in 0.5 N HCl (40 ml) was stirred for 2 days at room temperature. The mixture was neutralized with aq. $NaHCO_3$ and extracted with AcOEt, and the AcOEt extract was dried. Evaporation of the AcOEt afforded a powder of **10** (900 mg, 49%). IR ν_{max}^{KBr} cm^{-1}: 1670, 1596, 1535. To a suspension of the product **10** (203 mg) in dry THF (15 ml), NEt_3 (101 mg) and a solution of AcCl (79 mg) in dry THF (3 ml) were added at 0°. After separation of precipitates, the filtrate was evaporated to dryness under reduced pressure to obtain **11** (130 mg). The acetylation product **11** was chromatographed on silica gel (10 g) and eluted with $CHCl_3$–ethanol (15: 1). Recrystallization of **11** from AcOEt–hexane gave colorless needles, mp 141—142°/196—197°. *Anal.* Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.92; H, 6.06; N, 16.98. UV λ_{max}^{MeOH} nm (ε): 246 (8200), 280 (shoulder, 4700). IR ν_{max}^{KBr} cm^{-1}: 1668, 1640. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1679, 1643, 1612, 1545, 1481. MS *m/e*: 245 (M^+), 202, 163. NMR ($CDCl_3$): 2.13 (3H, s), 8.56 (1H, broad s), 9.47 (1H, broad s).

3-Acetamido-2-*tert*-butoxycarbonyl-4-oxo-4,5,6,7-tetrahydroindole (12)——Compound **7** (750 mg) was heated at 60° for 5 hr in a mixture of Ac_2O (15 ml) and anhyd. AcONa (300 mg). After having been worked up in the usual manner, the product **12** (800 mg, 91%) was recrystallized from AcOEt to colorless prisms of mp 217—218°. *Anal.* Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.59; H, 6.82; N, 9.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3415, 3255, 1700, 1690, 1650 (broad), 1582, 1522. NMR ($CDCl_3$): 1.55 (9H, s), 2.1 (2H, undefined), 2.13 (3H, s), 2.4 (2H, undefined), 2.80 (2H, t), 8.18 (1H, s), 10.58 (1H, s).

2-*tert*-Butoxycarbonyl-3-ethoxycarbonylamino-4-oxo-4,5,6,7-tetrahydroindole (13)——Ethyl chloroformate (2 ml) was added dropwise at 5—10° to a mixture of **7** (1.05 g) and pyridine (3 ml) in THF (10 ml). After stirring for 1 hr, the mixture was acidified with dil. HCl and then extracted with AcOEt. Evaporation of the AcOEt extract left a crystalline residue, which was recrystallized from benzene–ligroin to obtain colorless plates of **13** (800 mg, 59%), mp 163—164°. *Anal.* Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.88; H, 7.07; N, 8.60. NMR ($CDCl_3$): 1.27 (3H, t), 1.52 (9H, s), 2.14 (2H, broad q), 2.44 (2H, broad q), 2.80 (2H, t), 4.16 (2H, q), 7.50 (1H, s), 10.46 (1H, s).

3-Amino-2-*tert*-butoxycarbonyl-2-ethoxycarbonylmethyl-4-oxo-4,5,6,7-tetrahydroindole (14)——Ethyl bromoacetate (800 mg) was added to a mixture of **7** (1.1 g) and anhyd. K_2CO_3 (500 mg) in DMSO (20 ml), and stirred for 5 hr at room temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was chromatographed on alumina (50 g). Elution with benzene–$CHCl_3$ (1: 1) and evaporation of pure fraction gave a colorless oil (800 mg, 54%), which was crystallized from ligroin to colorless prisms, mp 103—104°. *Anal.* Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.74; H, 7.19; N, 8.24. UV λ_{max}^{EtOH} nm (ε): 254 (32000), 286 (11500). NMR ($CDCl_3$): 1.26 (3H, t), 1.51 (9H, s), 2.10 (2H, q), 2.32 (3H, undefined), 2.54 (2H, broad t), 4.16 (2H, q), 4.77 (2H, s), 5.66 (2H, s).

2-*tert*-Butoxycarbonyl-4-oxo-4,5,6,7-tetrahydroindole (16)——$NaNO_2$ (80 mg) was added in small portions with stirring at 5° to a solution of **7** (250 mg) in 20% HCl (7 ml).[13] After stirring at 5° for 20 min, the mixture was diluted with water and neutralized with solid $KHCO_3$ to pH *ca.* 8. The aq. mixture was shaken with AcOEt–*tert*-BuOH and the organic layer was washed with water and dried. Evaporation of the solvent afforded **15** (200 mg) as a yellow crystalline solid (mp 109—110°), which was refluxed for 15 min in ethanol (15 ml) containing 1 drop of conc. H_2SO_4. The reaction mixture was concentrated and the residue was partitioned between water and CH_2Cl_2. The CH_2Cl_2 soluble material was chromatographed on silica gel (20 g); elution with benzene–acetone (5: 1) gave the deaminated product (**16**, 80 mg), which was recrystallized from benzene–hexane to colorless plates of mp 182—184°. *Anal.* Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.60; H, 7.31; N, 5.90. MS *m/e*: 235 (M^+), 179, 162, 151 (base peak), 133, 123, 105, 57.

1-Ethoxycarbonylmethyl-3-formylamino-4-oxo-4,5,6,7-tetrahydroindole (19)——A solution of **14** (900 mg) in 98% formic acid (2.5 ml) was kept standing for 50 hr at room temperature. The mixture was diluted with water and neutralized with aq. $NaHCO_3$. The resulting precipitate was collected (600 mg) and chromatographed on silica gel (20 g); elution with benzene–acetone (3: 1) and evaporation of pure fractions gave crystalline **19** (450 mg, 64%). Recrystallization from benzene gave colorless needles of mp 191—192°. *Anal.* Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.10; H, 6.29; N, 10.59. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3160, 1730, 1680, 1630, 1570, 1550. NMR ($CDCl_3$): 1.27 (3H, t), 2.18 (2H, octet), 2.46 (2H, q), 2.68 (2H, t), 4.23 (2H, q), 4.52 (2H, s), 7.26 (1H, s), 8.32 (1H, s), 9.22 (1H, broad s).

2-*tert*-Butoxycarbonyl-1-ethoxycarbonylmethyl-3-formylamino-4-oxo-4,5,6,7-tetrahydroindole (17)——The mother liquor of **19**, which was described above, was concentrated and the residual **17** (25 mg) was purified by recrystallization from benzene–hexane; colorless plates of mp 144—148°. IR ν_{max}^{Nujol} cm^{-1}: 3220, 1745, 1680 (shoulder), 1655, 1560. NMR ($CDCl_3$): 1.33 (3H, t), 1.57 (9H, s), 2.1—2.8 (6H, m), 4.27 (2H, q), 5.00 (2H, s), 8.8 (1H, broad s), 9.0 (1H, broad s).

2,9-Dioxo-1,2,3,4,6,7,8,9-octahydro-5*H*-pyrido[3,2-*b*]indole (24)——a) Ethyl acrylate (3 ml) was added to a solution of **1** (6.0 g) and NaOEt (prepared from 1.0 g of sodium) in ethanol (70 ml). After heating at 60—70° for 2 hr, the mixture was concentrated *in vacuo*. The residue was diluted with water and extracted

with CH_2Cl_2–ethanol (3: 1). Evaporation of the extract afforded colorless crystals of **24** (2.0 g, 40%). Recrystallization from AcOEt–methanol gave colorless plates, mp 310°. *Anal.* Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.80, H, 5.97; N, 13.50. MS *m/e*: 204 (M^+), 176, 163, 162, 148, 134. UV λ_{max}^{EtOH} nm (ε): 249 (15200), 313 (3200). IR ν_{max}^{KBr} cm^{-1}: 3350, 3250—2800, 1670—1645, 1560, 1530. NMR (DMSO-d_6): 2.02 (2H, q), 2.28 (2H, m), 2.5—2.7 (6H, m), 8.06 (1H, s), 11.06 (1H, broad s).

The mother liquor of **24** was concentrated *in vacuo* and the residue (3.4 g) was chromatographed on alumina (80 g). Elution with $CHCl_3$ afforded **7** (100 mg) and a mixture of **22** and **23** (500 mg, approximately 2: 3 mixture on the basis of NMR spectrum). IR ν_{max}^{KBr} cm^{-1}: 1738, 1680, 1662, 1625. successively. A portion of this mixture of **22** and **23** (120 mg) was heated at 60° for 10 min with NaOEt (prepared from 150 mg of sodium) in ethanol (5 ml). The reaction mixture was concentrated, diluted with water and extracted with CH_2Cl_2–ethanol (3: 1). The organic layer was evaporated *in vacuo* to leave **24** (40 mg).

b) Ethyl acrylate (12 ml) was added dropwise at 0° to a mixture of **1** (24 g) and NaOEt (prepared from 4.0 g of sodium) in ethanol (280 ml). The mixture was stirred for 30 min at room temperature, and then heated at 58° for 1.5 hr under a nitrogen atmosphere. After having been worked up in the same way as a) above, **24** (6.4 g, 33%) was obtained by crystallization from CH_2Cl_2–ethanol. The mother liquor of **24** was concentrated, diluted with a small amount of AcOEt and allowed to stand overnight at room temperature to deposit crystalline **23** (1.6 g). Compound **23** was chromatographed on silica gel (100 g) and eluted with $CHCl_3$–ethanol (30: 1). Evaporation of pure fractions gave colorless flakes of **23**, mp 304—305° (changed to needles at *ca.* 200°). IR ν_{max}^{KBr} cm^{-1}: 1730, 1680, 1660, 1625. MS *m/e*: 304 (M^+), 245, 204, 149, 57 (base peak). The intermediate (**23**) was treated with HCl gas followed by water to give **24**. The mother liquor of **23** described above was concentrated *in vacuo* to precipitate **7**, which was collected and washed with benzene–hexane; yield 0.57 g. This was identical with an authentic sample of **7** in spectroscopic properties and TLC.

c) A stream of HCl gas was passed through a solution of **9** (1.5 g) in CH_3NO_2 (30 ml) at 0° for 30 min and then at room temperature for 1 hr. The mixture was evaporated *in vacuo*. The residue was diluted with water and extracted with AcOEt and then with $CHCl_3$–ethanol (15: 1). Evaporation of the combined extracts left **24** (780 mg, 78%). The product was identical with the authentic sample described above in IR spectrum.

7-Dimethyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydro-5*H*-pyrido[3,2-*b*]indole (25)——A mixture of **20** (2.96 g) and ethyl acrylate was heated with NaOEt in a manner similar to a) above. The crude product was chromatographed on silica gel (150 g); the column was eluted with $CHCl_3$–ethanol (60: 1) and then with benzene–acetone (5: 1). Evaporation of the latter fraction gave the desired product **25** (830 mg, 34%). Recrystallization from AcOEt–hexane gave colorless prisms of mp 235—238°. *Anal.* Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.07; H, 6.96; N, 11.95. MS *m/e*: 232 (M^+), 176, 148 (base peak). UV λ_{max}^{EtOH} nm (ε): 250 (13400), 313 (3250). NMR (DMSO-d_6): 1.02 (6H, s), 2.13 (2H, s), 2.53 (2H, s), 2.56 (2H, d), 2.70 (2H, d), 8.08 (1H, broad s), 11.02 (1H, broad s).

2,9-Dioxo-7-phenyl-1,2,3,4,6,7,8,9-octahydro-5*H*-pyrido[3,2-*b*]indole (26)——Compound **26** was also prepared in the same manner as the reaction (**20**→**25**). Recrystallization from AcOEt–hexane gave pale yellow prisms of mp 208—209°/236—237°. *Anal.* Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.58; H, 5.79; N, 9.79. MS *m/e*: 280 (M^+), 176 (base peak), 148, 119. UV λ_{max}^{EtOH} nm (ε): 249 (1400), 315 (3500). NMR (DMSO-d_6): 2.49 (2H, d), 2.57 (2H, d), 2.71 (2H, d), 2.90 (2H, d), 3.36 (1H, m), 7.27 (5H, s), 8.15 (1H, s), 11.17 (1H, broad s).

5-Ethoxycarbonylmethyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (27)——Ethyl bromoacetate (184 mg) was added dropwise to a mixture of **24** (204 mg) and anhyd. K_2CO_3 (200 mg) in dry DMSO (5 ml). The mixture was stirred for 2 hr at room temperature. After having been worked up in the usual way, the crude product (186 mg, 64%) was chromatographed on silica gel (10 g). Elution with $CHCl_3$–ethanol (30: 1), and evaporation of pure fractions gave **27** (160 mg). Recrystallization from $CHCl_3$–hexane gave colorless needles (100 mg) of **27**, mp 184—185°. *Anal.* Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.28; H, 6.28; N, 9.59. UV λ_{max}^{EtOH} nm (ε): 250 (17000), 310 (3000). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1745, 1675, 1563, 1540. NMR (DMSO-d_6): 1.21 (3H, t), 2.0 (2H, m), 2.2 (2H, m), 2.5 (2H, m), 2.63 (4H, t), 4.13 (2H, q), 4.70 (2H, s), 8.06 (1H, s).

5-(2-Ethoxycarbonylethyl)-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (28)——A mixture of ethyl acrylate (670 mg), **24** (1.02 g), anhyd. K_2CO_3 (850 mg), and DMSO (20 ml) was stirred for 5 hr at room temperature. The reaction mixture was diluted with 2 N HCl and extracted with CH_2Cl_2. Working up of the CH_2Cl_2 extract in the usual manner gave crude product, which was chromatographed on silica gel (30 g). Elution with $CHCl_3$–ethanol (50: 1) gave **28** (1.2 g). Recrystallization from $CHCl_3$–hexane gave colorless plates of **28** (1.03 g, 68%), mp 121°. *Anal.* Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.30; H, 6.74; N, 9.33. MS *m/e*: 304 (M^+, base peak), 275, 259, 231, 217, 203. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1725, 1680, 1645, 1620, 1540. NMR ($CDCl_3$): 1.24 (3H, t), 1.0—2.0 (6H, m), 2.65 (2H, t), 2.7 (4H, m), 4.05 (2H, t), 4.12 (2H, q), 7.93 (1H, broad s).

5-(2-Ethoxycarbonylethyl)-1-methyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (29)——NaOEt (prepared from 120 mg of sodium and 5 ml of ethanol) was added with stirring at 0° to an ethanol (40 ml) solution of **28** (1.55 g) and the mixture stirred for 45 min at room temperature. The solvent was

removed *in vacuo*, and, after suspending the residual solid in a mixture of dry benzene (50 ml) and Me_2SO_4 (640 mg), the reaction mixture was refluxed for 2 hr. After having been worked up in the usual manner, the product was chromatographed on silica gel (150 g). Elution with benzene–acetone (1: 1) gave **29** (300 mg) and **28** (500 mg) successively. Recrystallization of **29** from ether gave colorless plates, mp 105—106°. *Anal.* Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.40; H, 7.09; N, 8.66. UV λ_{max}^{EtOH} nm (ε): 250.5 (14400), 305 (3300). R $\nu_{max}^{CHCl_3}$ cm^{-1}: 2995, 1735, 1665, 1650, 1499. NMR ($CDCl_3$): 1.25 (3H, t), 2.13 (2H, octet), 2.46 (2H, sextet), 2.66 (2H, t), 2.6—2.9 (6H, m), 4.10 (2H, t), 3.47 (3H, s), 4.12 (2H, q).

5-Methyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (30)——To an ethanol (10 ml) solution of NaOEt (prepared from 96 mg of sodium) was added **24** (816 mg) at 0° and the mixture stirred for 15 min at room temperature. After complete evaporation of the solvent, the residual pale yellow powder was dissolved in a solution of Me_2SO_4 (500 mg) in benzene (20 ml). The solution was refluxed for 30 min and worked up in the usual way. The crude product was chromatographed on silica gel (50 g). Elution with $CHCl_3$–ethanol (60: 1) gave **30**, which was recrystallized from $CHCl_3$–petr. ether to give colorless needles of mp 234°. *Anal.* Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.21; H, 6.54; N, 12.95. MS *m/e*: 218 (M^+, base peak), 190, 176, 162, 148, 133. UV λ_{max}^{EtOH} nm (ε): 252 (15600), 313 (3210). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390, 1670, 1655, 1645, 1540. NMR ($CDCl_3$): 2.13 (2H, octet), 2.37 (2H, sextet), 2.6—2.9 (6H, m), 3.40 (3H, s), 7.87 (1H, broad s).

5-Ethyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (31)——Compound **31** was obtained by the reaction of **24** and Et_2SO_4 in a similar manner to that of **24**→**30**. Recrystallization from AcOEt–petr. ether gave colorless needles of mp 165°. *Anal.* Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.15; H, 6.94; N, 12.10. MS *m/e*: 232 (M^+, base peak), 203, 189, 176. UV λ_{max}^{EtOH} nm (ε): 213 (15100), 252 (16200), 312 (3200). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1680, 1660, 1645, 1543. NMR ($CDCl_3$): 1.32 (3H, t), 2.16 (2H, octet), 2.40 (2H, sextet), 2.70 (2H, t), 2.73 (2H, t), 2.75 (2H, t), 3.79 (2H, q), 7.92 (1H, broad s).

5-Benzyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (32)——To a mixture of **24** (4.86 g), anhyd. K_2CO_3 (4.1 g), and DMSO (50 ml) was added benzyl chloride (3.0 g), and the mixture heated at 95° for 5 hr under a nitrogen atmosphere. After dilution with water, the mixture was extracted with CH_2Cl_2 and the extract was dried. The solvent was removed *in vacuo* and the residual solid was washed with dry ether to obtain **32** as colorless flakes (5.6 g), mp 182—183°. *Anal.* Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.47; H, 6.25; N, 9.48. UV λ_{max}^{EtOH} nm (ε): 255 (18500), 310 (3300). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390, 1685, 1658, 1647, 1535. NMR ($CDCl_3$): 2.09 (2H, octet), 2.37 (2H, sextet), 2.5—2.8 (6H, m), 4.93 (2H, s), 6.88—7.38 (5H, m), 7.72 (1H, s).

5-Benzyl-1-methyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (33)——Compound **32** (430 mg) was added to a solution of sodium (34 mg) in ethanol (10 ml) in an ice bath. The bath was removed and the mixture was stirred for 30 min. The resulting solution was evaporated *in vacuo* to complete dryness (a trace of ethanol was azeotropically removed with benzene). Benzene (20 ml) and Me_2SO_4 (185 mg) were added to the yellow, amorphous residue. The mixture was refluxed for 1 hr. After having been worked up, the product was extracted with CH_2Cl_2. The CH_2Cl_2 was evaporated and the residue was chromatographed on silica gel (40 g). Elution with $CHCl_3$–EtOH (60: 1) gave 400 mg of **33**. Recrystallization from $CHCl_3$–hexane afforded colorless flakes of **33** (320 mg), mp 166—167°. *Anal.* Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.83; H, 6.64; N, 9.06. UV λ_{max}^{EtOH} nm (ε): 251 (16000), 305 (3550).

1-Methyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (34)——To a stirred solution of **24** (377 mg) in liq. NH_3 (10 ml) was added sodium (118 mg) at −58° and the mixture was stirred for 30 min. Ammonium chloride (332 mg) was added to the mixture and the NH_3 was removed. The residue was partitioned between water and CH_2Cl_2, and the CH_2Cl_2 layer was washed with water and dried. Chromatography of the product on silica gel (20 g) using $CHCl_3$–ethanol (60: 1) as eluent afforded **34** as colorless plates (80 mg), mp 234—235°. UV λ_{max}^{EtOH} nm (ε): 247 (11600), 306 (3100). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1655, 1645, 1485. NMR ($CDCl_3$): 2.10 (2H, q), 2.47 (2H, t), 2.6—2.9 (6H, m), 3.48 (3H, s), 10.18 (1H, broad s).

5-Acetyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (35)——To a suspension of **24** (1 g) in Ac_2O (25 ml) was added anhyd. NaOAc (500 mg) and the mixture was stirred at 84° for 7 hr. After cooling, the mixture was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and dried. After removal of the solvent, the residue was chromatographed on silica gel (50 g). Elution with $CHCl_3$–ethanol (50: 1) gave **35** (520 mg). Recrystallization from $CHCl_3$–ligroin gave pale yellow needles, mp 154—155°. *Anal.* Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.34; H, 5.63; N, 11.48. MS *m/e*: 246 (M^+), 204 (base peak), 203, 176, 162, 148, 134. UV λ_{max}^{EtOH} nm (ε): 255 (24000), 290 (shoulder, 6650), 330 (shoulder, 233). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3365, 1715, 1685, 1660, 1527. NMR ($CDCl_3$): 2.14 (2H, octet), 2.3—2.6 (4H, m), 3.08 (4H, broad q), 2.51 (3H, s), 8.03 (1H, broad s).

1,5-Diacetyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (36)——The diacetyl derivative (**36**) was prepared in *ca.* 60% yield by acetylation of **24** with Ac_2O–AcONa at 160—170° (bath temperature). The crude product was chromatographed on silica gel using $CHCl_3$–ethanol (50: 1) as eluent. Compound **36** thus isolated was recrystallized from $CHCl_3$–ligroin to colorless plates, mp 195°. *Anal.* Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.55; H, 5.32; N, 9.67. MS *m/e*: 288 (M^+), 245, 204 (base peak), 172, 162, 148. UV λ_{max}^{EtOH} nm (ε): 249 (9000), 300 (shoulder, 1000). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1675, 1620,

1530. NMR ($CDCl_3$): 2.19 (2H, octet), 2.43 (2H, sextet), 2.57 (3H, s), 2.7 (2H, undefined), 2.72 (3H, s), 3.08 (4H, broad t).

5-*p*-Chlorobenzoyl-2,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3,2-*b*]indole (37)——To an ethanol (20 ml) solution of NaOEt (prepared from 115 mg of sodium) was added **24** (1.02 g) at 0°. After the solution was stirred for *ca.* 30 min at room temperature, the solvent was removed *in vacuo*. The residue was dissolved in dry THF (20 ml) and treated with *p*-chlorobenzoyl chloride (900 mg) in dry THF (10 ml). The reaction mixture was heated at 70—80° for 2 hr. The crude product was chromatographed on silica gel (50 g) using $CHCl_3$–ethanol (15: 1) as eluent to obtain pale yellow needles of **36** (850 mg, 53%), mp 203—204°. *Anal.* Calcd. for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; Cl, 10.34; N, 8.17. Found: C, 62.98; H, 4.31; Cl, 10.56; N, 8.01. MS *m/e*: 344 (M^++1), 342 (M^+), 341 (M^+−1), 141, 140, 139 (base peak), 112. UV λ_{max}^{EtOH} nm (ε): 266 (25000). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380, 1685, 1660, 1590, 1525. NMR ($CDCl_3$): 2.11 (2H, q), 2.46 (2H, t), 2.6—2.7 (4H, m), 2.75 (2H, d), 7.48 (2H, d), 7.67 (2H, d), 8.04 (1H, broad s).

2,9-Dioxo-1,2,6,7,8,9-hexahydro-5*H*-pyrido[3,2-*b*]indole (38)——A solution of DDQ (300 mg) in dioxane (10 ml) was added dropwise at 100° to a suspension of **24** (240 mg) in dioxane (30 ml). After heating for further 10 min, the brown precipitates were collected and extracted with hot AcOEt to remove the hydroquinone compound; the insoluble part was then extracted with hot ethanol. The ethanolic solution was evaporated and the residual product (**38**) was recrystallized from dimethylformamide (DMF) to obtain prisms, mp>300° (116 mg). *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.09; H, 5.08; N, 13.98. UV λ_{max}^{EtOH} nm: 232, 254.5. IR ν_{max}^{KBr} cm^{-1}: 1630 (broad). NMR (DMSO-d_6): 2.07 (2H, quintet, J=6 Hz), 2.38 (2H, t, J=6 Hz), 2.86 (2H, t, J=6 Hz), 6.05 (1H, d, J=10 Hz), 7.54 (1H, d, J=10 Hz), 11.88 (1H, mound).

3-Amino-2-(2-ethoxycarbonylethyl)-4-oxo-4,5,6,7-tetrahydroindole (39) and Its 3-Acetamido Derivative (40)——To a solution of **24** (1.0 g) in ethanol (35 ml) was added 5% ethanolic HCl (15 ml) and the mixture was stirred for 13 hr at room temperature. The solvent was evaporated and the residue was dissolved in dry benzene. The solvent was then azeotropically removed. The residual yellow powder of **39** (*ca.* 1.2 g) was suspended in dry THF (80 ml) containing NEt_3 (580 mg). After addition of AcCl (452 mg), the mixture was stirred for 1 hr at room temperature. After having been worked up in the usual manner, the product was crystallized from $CHCl_3$–hexane to colorless flakes of **40** (520 mg), mp 165°. *Anal.* Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.70; H, 6.96; N, 9.55. UV λ_{max}^{EtOH} nm (ε): 247 (8800), 282 (3650). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1710, 1675, 1640, 1605, 1539.

3-Amino-2-*tert*-butoxycarbonyl-4-ethoxycarbonyl-5-methylpyrrole (44)——a) MVK (2 ml) was added at 15° to a solution of the enaminonitrile (**41**, 27 g) and NaOEt (prepared from 2.5 g of sodium) in ethanol (150 ml); the solution was stirred for 15 min, concentrated, and diluted with water. The resulting crystals of **44** were collected, washed with water, and dried. The product weighed 26.5 g (96%). Recrystallization from AcOEt gave colorless prisms of mp 193°. *Anal.* Calcd. for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.35; H, 7.65; N, 10.39. MS *m/e*: 268 (M^+), 223, 212 (base peak), 195, 194, 167, 166, 122, 121. UV λ_{max}^{EtOH} nm (ε): 236.5 (34300), 280 (13600). IR ν_{max}^{Nujol} cm^{-1}: 3490, 3370, 3260, 1685, 1640, 1580. NMR ($CDCl_3$): 1.35 (3H, t), 1.60 (9H, s), 2.46 (3H, s), 4.29 (2H, q), 5.45 (2H, broad s), 9.85 (1H, broad s).

b) A mixture of **48** (20 mg), dimethylformamide (1 ml), and NaH (50% oil dispersion, 20 mg) was stirred at 70° for 30 min. The reaction mixture was successively diluted with CH_2Cl_2, water, and aq. HCl. The organic layer was washed with water and dried. Evaporation of the solvent left 12 mg of crystalline **44**; the product was identified with the one described above a) (IR and TLC).

3-Amino-4-benzoyloxycarbonyl-2-*tert*-butoxycarbonyl-5-methylpyrrole (45)——The enaminonitrile (**42**, 2.4 g) was allowed to react with MVK (0.8 ml) at 0° in the presence of NaOEt (prepared from 450 mg of sodium) in ethanol (10 ml). The reaction mixture was worked up as above; the product **45** was crystallized from benzene–hexane to give colorless plates of mp 181—182° (sintered at 165°); yield 900 mg. *Anal.* Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.55; H, 6.85; N, 8.51. IR ν_{max}^{KBr} cm^{-1}: 3550, 3430, 3300, 1685, 1650, 1600, 1560, 1525, 1500. NMR ($CDCl_3$): 1.57 (9H, s), 2.43 (3H, s), 5.2 (2H, broad s), 7.26—7.81 (5H, m), 9.60 (1H, broad s).

2-Carboxy-4-ethoxycarbonyl-5-methylpyrrole (46)——A mixture of $NaNO_2$ (95 mg) and **44** (270 mg) in 4 N HCl (6 ml) was stirred for 1 hr at room temperature. The mixture was neutralized with solid $NaHCO_3$ and extracted with AcOEt–*tert*-BuOH. The AcOEt layer was washed with water and dried. The solvent was removed *in vacuo* to leave a reddish oil (350 mg), to which ethanol (25 ml)–conc. H_2SO_4 (2 drops) was added and the mixture was gently refluxed for 30 min. The reaction mixture was concentrated, diluted with water, and extracted with CH_2Cl_2. The product was chromatographed on silica gel (5 g). Elution with $CHCl_3$ afforded the *tert*-butyl ester of **46** (100 mg), which was recrystallized from AcOEt–hexane to colorless plates of mp 178°. MS *m/e*: 253 (M^+), 208, 197 (base peak), 180, 169, 168, 152, 151, 150, 134, 57. IR ν_{max}^{Nujol} cm^{-1}: 3270, 1700, 1670, 1570.

The above *tert*-butyl ester of **46** (95 mg) was stirred for 1.5 hr in 99% formic acid (3 ml) at room temperature. After dilution of the reaction mixture with water, the resulting precipitate was collected and washed with water to obtain crystalline **46** (60 mg), which was recrystallized from benzene–acetone to pale yellow prisms, mp 238—240°. MS *m/e*: 197 (M^+), 169, 168, 152, 151, 150, 134 (base peak), 78, 51. IR ν_{max}^{Nujol} cm^{-1}: 3270, 1665, 1580. This product was identified with an authentic specimen of **46**.[15]

***tert*-Butyl-2,4-dicyano-2-(2-ethoxycarbonyl-1-methylvinylamino)butyrate (47)**——A mixture of **41** (2.0 g), acrylonitrile (0.8 ml), NEt_3 (0.5 ml), and *tert*-BuOH (15 ml) was allowed to stand at room temperature for 5 days. Evaporation of the solvent left an oil, which crystallized on standing. The crystals were collected and washed with ether–hexane to obtain **47** (1.7 g, 71%). Recrystallization from ether–hexane gave an analytical sample of colorless plates, mp 83°. *Anal.* Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21; N, 13.08. Found: C, 59.93; H, 7.15; N, 13.16.

5-*tert*-Butoxycarbonyl-5-(2-cyanoethyl)-3-ethoxycarbonyl-4-imino-2-methyl-2-pyrroline (48)——A mixture of **47** (200 mg), NEt_3 (1 ml), and *tert*-BuOH (15 ml) was refluxed for 5 hr. After having been worked up in the usual way, the product was recrystallized from ether–hexane to obtain colorless plates of **48**, mp 112—113° (150 mg, 75%). *Anal.* Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21; N, 13.08. Found: C, 59.85; H, 7.16; N, 13.06.

7a-*tert*-Butoxycarbonyl-3-ethoxycarbonyl-2-methyl-5-oxo-5,6,7,7a-tetrahydro-1*H*-pyrido[3,2-*b*]pyridine (49)——Ethyl acrylate (2.5ml) and **41** (4.0 g) were allowed to react at 0° for 1.5 hr. The reaction mixture was neutralized with 2 N HCl to pH *ca.* 8 and concentrated. The residue was extracted with CH_2Cl_2, and the solution was evaporated *in vacuo* to leave **49** (2.5 g), which was recrystallized from CH_2Cl_2–hexane to give colorless prisms, mp 120°. *Anal.* Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.50; H, 6.97; N, 8.53. MS *m/e*: 322 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3100 (broad), 1725, 1695, 1630, 1550. NMR ($CDCl_3$): 1.36 (3H, t), 1.44 (9H, s), 1.7 (1H, m), 2.7 (2H, m), 2.9 (1H, m), 4.43 (2H, q), 9.20 (1H, s).

3-Benzyloxycarbonyl-7a-*tert*-butoxycarbonyl-2-methyl-5-oxo-5,6,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine (50)——Ethyl acrylate (1.2 ml) was allowed to react with **42** (24 g) at 0° for 50 min in the presence of NaOEt (two molar equivalents). The reaction mixture was neutralized with 2 N HCl to pH 8—9 and concentrated. The residue was partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was washed with water and dried. Evaporation of the solvent left **50**, which was crystallized from ether–hexane to colorless needles of **50**, mp 103° (1.5 g). *Anal.* Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.43; H, 6.02; N, 7.22.

3-Ethoxycarbonyl-2-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine (51)——Ethyl acrylate (0.6 ml) was added at 0° to a mixture of **41** (1 g) and NaOEt (prepared from 200 mg of sodium) in ethanol. The mixture was stirred for 30 min at room temperature and then heated at 60—70° for 1 hr. Working up in the usual way gave **51** (200 mg); recrystallizations from CH_2Cl_2–hexane afforded a pure sample, mp 164—166°. *Anal.* Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.49; H, 6.51; N, 12.62. MS *m/e*: 222 (M^+), 193, 177, 176, 175, 149, 148, 28 (base peak). UV λ_{max}^{EtOH} nm (ε): 229 (16000), 291 (4800). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435, 3250, 1665, 1530, 1516. NMR ($CDCl_3$): 1.34 (3H, t), 2.46 (3H, s), 2.7 (4H, m), 4.27 (2H, q), 8.00 (1H, s), 9.35 (1H, broad s).

The mother liquor of **51** described above deposited crystals of **49** (300 mg) when kept standing for a few days. Recrystallization from CH_2Cl_2–hexane or benzene–hexane gave colorless prisms of **49**, mp 120°.

Transformation of 49 into 51 and 44——a) A solution of **49** (500 mg) in formic acid (2.5 ml) was allowed to stand at room temperature for 20 hr. The mixture was diluted with water, neutralized with aq. Na_2CO_3 solution, and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated. The crystalline residue was washed with AcOEt–hexane to give 300 mg of **51**.

b) A mixture of **49** (600 mg) and xylene (6 ml) was heated for 4.5 hr in an oil bath of 170—190°. After evaporation of the solvent, the residue was crystallized from AcOEt–hexane to yield 200 mg of **51**.

c) To a 10% ethanolic NaOEt solution (7 ml) was added **49** (300 mg), and the mixture was heated at 60—70° for 3 hr. The reaction mixture was concentrated and the residue was partitioned between water and CH_2Cl_2. The CH_2Cl_2 soluble part was chromatographed on silica gel (7 g). Elution with $CHCl_3$–ethanol (20: 1) afforded **44** (150 mg) and **49** (30 mg), successively. The column was then eluted with $CHCl_3$–ethanol (10: 1) to obtain **51** (60 mg).

d) Compound **49** (640 mg) was heated at 150—170° for 30 min. After cooling, the crystalline product (460 mg) was washed with CH_2Cl_2–hexane to afford **51** (340 mg).

3-Benzyloxycarbonyl-2-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*b*]pyridine (52)——a) A solution of **50** (700 mg) in formic acid (3 ml) was stirred for 7 hr at room temperature. The solution was diluted with water, neutralized with Na_2CO_3 and extracted with CH_2Cl_2. Evaporation of the solvent left crystalline **52** (400 mg), which was recrystallized from AcOEt–methanol to colorless prisms, mp 189—190°. *Anal.* Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.64; H, 5.61; N, 9.84. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3250, 1675, 1545, 1515. NMR (DMSO-d_6): 2.36 (3H, s), 2.5—2.8 (4H, m), 5.23 (2H, s), 7.3 (5H, m), 7.96 (1H, s), 11.03 (1H, broad s).

b) Compound **50** was heated in xylene in the same way as described above for **51**, giving **52**.

3-Ethoxycarbonyl-2-methyl-5-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine (53)——Chloranil (720 mg) was added to a solution of **51** (500 mg) in benzene (10 ml)–dioxane (10 ml). After heating at 80° for 20 min, the solvent was removed and the residue was washed with benzene and then with $CHCl_3$. The crude product (400 mg) thus obtained was chromatographed three times on alumina (10 g) using $CHCl_3$–ethanol as solvent to obtain **53** (180 mg); pale yellow plates, mp 214—215°. *Anal.* Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.97; H, 5.47; N, 12.55. MS *m/e*: 220 (M^+, base peak), 174, 146, 118. UV λ_{max}^{EtOH} nm (ε): 225 (15900), 254 (shoulder, 7000), 259 (7100), 333 (15800). IR ν_{max}^{Nujol} cm^{-1}: 1680, 1620. NMR (DMSO-d_6):

1.32 (3H, t), 2.03 (3H, s), 4.32 (2H, q), 6.08 (1H, d, J=10 Hz), 7.57 (1H, d, J=10 Hz), 9.96 (1H, s), 11.92 (1H, s).

5-Cyano-3-ethoxycarbonyl-5-(2-ethoxycarbonylethyl)-2-methyl-4-oxo-2-pyrroline (58)——Ethyl acrylate (2.1 ml) was added at 0° to a solution of the enaminonitrile (54) and NaOEt (prepared from 1.28 g of sodium) in ethanol (100 ml). After having been reacted at 0° for 20 min, the solution was then stirred for an additional 20 min at room temperature. After cooling, the solution was acidified with dil. HCl to pH 4, concentrated, and diluted with water. The resulting precipitate was collected and washed with water to obtain **58** (5.4 g, 71%). Recrystallization from AcOEt gave colorless fine plates, mp 163—165°. *Anal.* Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.17; N, 9.52. Found: C, 57.07; H, 6.17; N, 9.43. MS *m/e*: 236 (M^+), 222, 221, 207 (base peak), 203, 194, 175, 161, 149, 148, 93, 67, 55. UV λ_{max}^{EtOH} nm (ε): 236 (13500), 299 (8500). IR ν_{max}^{Nujol} cm^{-1}: 3220, 2250, 1735, 1710, 1650. NMR ($CDCl_3$): 1.24 (3H, t), 1.33 (3H, t), 2.2—2.6 (4H, m), 2.68 (3H, s), 4.13 (2H, q), 4.27 (2H, q).

5-Cyano-5-(2-cyanoethyl)-3-ethoxycarbonyl-2-methyl-4-oxo-2-pyrrole (59)——a) Acrylonitrile (1.2 ml) was added at −6° to a mixture of **54** (2.40 g) and NaOEt (prepared from 460 mg of sodium and 50 ml of ethanol). The reaction mixture was stirred at 0° for 30 min. After having been acidified to pH 5.5 with dil. HCl, the mixture was concentrated, diluted with water, and treated with dil. HCl to adjust to pH 3. The resulting precipitate was collected and recrystallized from AcOEt to colorless plates of **59** (1.14 g, 46%), mp 202.5—204.5° (dec.). *Anal.* Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.33; H, 5.15; N, 17.21. MS *m/e*: 247 (M^+), 207 (base peak), 202, 179, 161, 93, 67, 39, 29, 28. UV λ_{max}^{EtOH} nm: 238, 301. IR ν_{max}^{Nujol} cm^{-1}: 3225, 2250, 1710, 1640, 1530, 1510. NMR (DMSO-d_6): 1.23 (3H, t), 2.17—2.77 (4H, m), 2.50 (3H, s), 4.10 (2H, q), 8.83 (1H, broad s).

b) Compound **61** (60 mg) was mixed with an ethanolic solution of NaOEt (prepared from 15 mg of sodium and 3 ml of ethanol). Acrylonitrile (0.2 ml) was added to the solution under ice-cooling. After stirring for 50 min, the reaction mixture was acidified with 0.2 N HCl to pH 4 and concentrated. The residue was diluted with water, and the insoluble **59** was collected and washed with water; yield 40 mg (52%). The product was identified with the specimen described above a) (IR and TLC).

5-Cyano-3-ethoxycarbonyl-5-(2-ethoxycarbonylethyl)-2-methyl-4-oxo-2-pyrroline (60)——MVK (0.6 ml) was added dropwise at 0° to a mixture of **54** (960 mg) and NaOEt (prepared from 230 mg of sodium) in ethanol (20 ml) and the mixture was stirred for 20 min. After having been worked up as described above, the product (**60**, 660 mg) was recrystallized from AcOEt to give give colorless needles of mp 172—177°. *Anal.* Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.96; H, 6.12; N, 10.62. MS *m/e*: 264 (M^+), 219, 207, 194, 161, 149, 148 (base peak), 93, 67, 43. UV λ_{max}^{EtOH} nm: 238, 299. IR ν_{max}^{Nujol} cm^{-1}: 3230, 2250, 1720, 1710, 1645, 1535, 1515. NMR ($CDCl_3$): 1.33 (3H, t), 2.17—2.67 (4H, m), 2.17 (3H, s), 2.67 (3H, s), 4.27 (2H, q), 9.30 (1H, broad s).

2-Cyano-4-ethoxycarbonyl-3-hydroxy-5-methylpyrrole (61)——a) To a solution of **54** (240 mg) and acrylonitrile (0.1 ml) in dry DMSO (1 ml) was added a solution (0.7 ml) of dimsyl sodium [prepared from DMSO (1.5 ml) and NaH (50% oil dispersion, 200 mg)] under ice-cooling.[17] After stirring at room temperature for 1.5 hr, the reaction mixture was diluted with water, adjusted to pH 3 with aq. HCl, and extracted with AcOEt. After evaporation of the AcOEt, the residue was chromatographed on silica gel (5 g). Elution with benzene–acetone (10: 1) gave pure **61** (125 mg, 64%), mp 179—181°. *Anal.* Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.51; H, 5.31; N, 14.36. IR ν_{max}^{Nujol} cm^{-1}: 3240, 2215. UV λ_{max}^{EtOH} nm (ε): 224 (31400), 242 (shoulder, 14900).

b) Compound **59** (80 mg) was added at room temperature to dimsyl sodium prepared from NaH (50 mg) and DMSO (1 ml). After stirring for 1 hr, the mixture was diluted with water, acidified with 1 N HCl to pH 3, and extracted with AcOEt. Crude **61** thus obtained was chromatographed on silica gel (5 g); elution with benzene–acetone (10: 1) gave 30 mg of pure **61**. The product was identified with the one described above a) (IR and TLC).

3-Amino-4-ethoxycarbonyl-2-isopropyloxycarbonyl-5-methylpyrrole (62)——MVK (0.9 ml) was added dropwise at 0° to a mixture of NaOEt (prepared from 400 mg of sodium) and **55** (2.2 g) in ethanol (30 ml). After stirring at 0° for 30 min, the reaction mixture was concentrated and the residue was partitioned between water and AcOEt. The AcOEt layer was washed with water, dried, and evaporated. The resulting crystalline product was washed with AcOEt–hexane to obtain **62** (400 mg, 18%). Recrystallization from benzene gave colorless needles of **62**, mp 161—162°. *Anal.* Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.61; H, 7.24; N, 10.98. NMR ($CDCl_3$): 1.4—1.6 (6H, m), 2.46 (3H, s), 4.30 (2H, q), 5.22 (1H, quintet), 5.3 (2H, broad s), 9.7 (1H, mound).

3-Amino-4-ethoxycarbonyl-2-isooctyloxycarbonyl-5-methylpyrrole (63)——The isooctyl ester (**63**) was prepared in 37% yield in the same manner as above. Recrystallization from hexane gave colorless plates of **63**, mp 91—92°. *Anal.* Calcd. for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70; N, 8.64. Found: C, 62.89; H, 8.71; N, 8.55. NMR ($CDCl_3$): 0.81 (3H, broad t), 1.2—1.5 (18H, overlapped signals), 2.46 (3H, s), 4.28 (2H, q), 5.13 (1H, q), 5.40 (2H, mound), 10.0 (1H, mound).

3-Acetoxy-2-cyano-4-ethoxycarbonyl-2-(2-ethoxycarbonylethyl)-5-methyl-2*H*-pyrrole (65)——The pyrrolinone (**58**, 294 mg) was stirred at 60° for 16 hr in a mixture of Ac_2O (2 ml) and AcONa (100 mg). The reaction mixture was concentrated, diluted with water, and extracted with AcOEt. The AcOEt was removed

in vacuo; the residue was chromatographed on silica gel (10 g) using benzene–acetone (9: 1) as eluent to obtain **65** (160 mg, 48%) as a pale yellow oil. MS *m/e*: 336 (M^+). UV λ_{max}^{EtOH} nm: 226.5, 298.5. IR $\nu_{max}^{liq.}$ cm^{-1}: 2250, 1740, 1725, 1560. NMR ($CDCl_3$): 1.25 (3H, t), 1.38 (3H, t), 2.37—2.73 (4H, m), 2.60 (3H, s), 3.00 (3H, s), 4.00—4.37 (4H, m).

5-Cyano-3-ethoxycarbonyl-5-ethoxycarbonylethyl-2-methyl-4-oxo-2-pyrroline (66) or 2-cyano-4-ethoxycarbonyl-2-(2-ethoxycarbonylethyl)-3-methoxy-5-methyl-2*H*-pyrrole (67)——A mixture of **58** (294 mg), methyl iodide (0.7 ml), and anhyd. K_2CO_3 (150 mg) in acetone (10 ml) was heated at 60° for 50 min. The reaction mixture was concentrated and the residue was extracted with AcOEt. After the AcOEt layer was washed with water and dried, the solvent was removed *in vacuo* to leave a colorless oil (**66** or **67**, 290 mg, 94%). MS *m/e*: 308 (M^+), 264, 263, 217, 208, 163, 162 (base peak), 136, 67, 55. UV λ_{max}^{EtOH} nm: 242.5, 314. IR $\nu_{max}^{liq.}$ cm^{-1}: 2980, 2250, 1735, 1690, 1535. NMR ($CDCl_3$): 1.23 (3H, t), 1.33 (3H, t), 2.40 (4H, broad s), 2.67 (3H, s), 3.23 (3H, s), 4.13 (2H, q), 4.23 (2H, q).

5-(2-Carboxyethyl)-5-cyano-3-ethoxycarbonyl-2-methyl-4-oxo-2-pyrroline (68)——A solution of **58** (750 mg) in 10% methanolic KOH (10 ml) was stirred at room temperature for 1 hr. The reaction mixture was cooled to 0° and acidified with aq. HCl to pH 2.5, and concentrated; the resulting crystalline **68** was washed with water and recrystallized from ethanol to colorless plates (300 mg) of mp 190—192°. MS *m/e*: 266 (M^+).

7a-Cyano-3-ethoxycarbonyl-2-methyl-5-oxo-5,6,7,7a-tetrahydropyrano[3,2-*b*]pyrrole (69)——DCC (455 mg) was added to a solution of **68** (532 mg) in CH_2Cl_2 (30 ml) and the mixture was stirred for 1 hr at room temperature. After the removal of an insoluble material, the CH_2Cl_2 solution was washed with water and evaporated. The residual product was chromatographed on silica gel (15 g). Elution with benzene–acetone (10: 1) afforded **69** (300 mg, 61%) as a yellow oil. MS *m/e*: 248 (M^+), 220. UV λ_{max}^{EtOH} nm: 227, 287. IR $\nu_{max}^{liq.}$ cm^{-1}: 2230, 1770, 1740, 1705, 1565. NMR ($CDCl_3$): 1.33 (3H, t); 2.2—2.8 (4H, m), 2.90 (3H, s), 4.30 (2H, q).

Ethanol (0.5 ml) saturated with HCl was added to a solution of **69** (0.11 g) in ethanol (1.5 ml) and the mixture was stirred for 1 hr at room temperature. The mixture was diluted with water, neutralized with aq. NaOH, and concentrated. The residual crystalline product was collected and washed with water to give **58** (70 mg).

3-Amino-2-carbamoyl-4-ethoxycarbonyl-5-methylpyrrole (73)——Ethyl acrylate (0.5 ml) was added dropwise at 0° to a mixture of **70** (1.1 g) and NaOEt (prepared from 250 mg of sodium) in ethanol (40 ml), and the reaction mixture was stirred for 1 hr. After cooling, the mixture was partitioned between water and AcOEt. The organic layer was washed with water, dried, and evaporated to leave black-purple crystals, which were collected and washed with benzene to obtain **73** (300 mg). Recrystallizations from AcOEt and then from AcOEt–methanol gave colorless plates, mp 229—230°. MS *m/e*: 211 (M^+), 194, 165, 148 (base peak), 120, 92, 67. UV λ_{max}^{EtOH} nm: 236.5, 281. NMR (DMSO-d_6): 1.27 (3H, t), 2.36 (3H, s), 4.19 (2H, q), 5.66 (2H, broad s). 6.61 (2H, broad s), 10.9 (1H, mound).

3-Amino-4-ethoxycarbonyl-5-methyl-2-methylcarbamoylpyrrole (74)——MVK (0.9 ml) was added dropwise at 0° to a mixture of **71** (2.04 g) and NaOEt (prepared from 450 mg of sodium) in ethanol (60 ml). After stirring for 1 hr at room temperature, the reaction mixture was concentrated and the residue was partitioned between water and AcOEt. The organic layer was washed with water and dried. Evaporation of the solvent left crystalline **74**, which was collected and washed with AcOEt (yield 1.2 g). Recrystallization from ethanol gave colorless prisms, mp 213—215°. *Anal.* Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.32; H, 6.62; N, 18.60. UV λ_{max}^{EtOH} nm: 235.5, 280. NMR (DMSO-d_6): 1.30 (3H, t), 2.36 (3H, s), 2.74 (3H, d), 4.20 (2H, q), 5.60 (2H, s), 6.95 (1H, d), 10.77 (1H, broad s).

3-Amino-2-N,N-cyclopentamethylenecarbamoyl-4-ethoxycarbonyl-5-methylpyrrole (75)——A mixture of **72** (960 mg) and NaOEt (prepared from 200 mg of sodium) in ethanol (25 ml) was stirred at room temperature for 1 hr. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with water, dried, and evaporated to leave **75** (700 mg, 73%). Recrystallization from benzene gave colorless prisms of mp 158—159°. *Anal.* Calcd. for $C_{14}H_{21}N_3O_3$: C, 60.19; H, 7.58; N, 15.04. Found: C, 60.04; H, 7.57; N, 14.80. NMR (DMSO-d_6): 1.27 (3H, t), 1.55 (6H, broad s), 2.35 (3H, s), 3.41 (4H, broad s), 4.20 (2H, q), 5.13 (2H, s), 10.91 (1H, mound).

3-Acetamino-4-ethoxycarbonyl-5-methyl-2-methylcarbamoylpyrrole (76)——Acetylation of **74** with Ac_2O at 80° for 30 min followed by usual work-up gave **76** in a quantitative yield. Compound **76** was recrystallized from ethanol to colorless plates of mp 243—245° (turned to needles at *ca.* 200°). *Anal.* Calcd. for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 54.07; H, 6.29; N, 15.48. IR ν_{max}^{Nujol} cm^{-1}: 3310, 3180, 1695, 1650, 1625.

4-Ethoxycarbonyl-3-ethoxycarbonylamino-5-methyl-2-methylcarbamoylpyrrole (77) and 7-Ethoxycarbonyl-3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (78)——Ethyl chloroformate (2 ml) was added dropwise at 0° to a solution of **74** (1.05 g) and pyridine (3 ml) in dry THF (15 ml). After 30 min, the reaction mixture was treated with aq. HCl. The resulting precipitate was collected and washed with water to obtain **77** (1.1 g) as colorless crystals, mp 235°/305°. A mixture of **77** (1.0 g) and NaOEt (prepared from 250 mg of sodium) in ethanol (20 ml) was stirred at room temperature; colorless crystals deposited in a few minutes. After 3 hr, the reaction mixture was acidified with dil. HCl to pH 3 and the precipitate was collected and washed with water (850 mg). The product was recrystallized from 80% aq. AcOH to colorless plates of **78** (600 mg), mp 305°. *Anal.* Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.58; H, 5.22; N, 16.73.

Found: C, 52.62; H, 5.12; N, 16.70. MS *m/e*: 251 (M^+, base peak), 206, 205, 204, 177, 176, 175, 148, 122. UV λ_{max}^{EtOH} nm (ε): 229.5 (30200), 270 (10150). UV $\lambda_{max}^{0.1N\ HCl}$ nm: 231, 274. UV $\lambda_{max}^{0.1\ NaOH}$ nm: 242, 285. NMR (CF_3CO_2D): 1.48 (3H, t), 2.72 (3H, s), 3.58 (3H, s), 4.56 (2H, q).

7-Ethoxycarbonyl-3,6-dimethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydro-1*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (79) A mixture of **74** (230 mg), potassium xanthogenate (190 mg), and pyridine (4 ml) was heated at 90° for 1 hr. After evaporation of the pyridine, the crystalline residue was mixed with a few milliliters of 30% aq. DMF. The mixture was acidified with AcOH and the precipitated crystals were collected and washed with water (190 mg, 70%). Recrystallization from ethanol gave colorless plates of **79**, mp 257°. *Anal.* Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.42; H, 4.90; N, 15.72. Found: C, 49.35; H, 4.70; N, 15.60. UV λ_{max}^{EtOH} nm: 227, 261.5, 300. IR ν_{max}^{Nujol} cm^{-1}: 3460, 3360, 1680, 1670, 1580.

In order to confirm the structure of **79**, **79** was desulfurized to **80**. Thus, a mixture of **79** (20 mg), Raney Ni (W-4, 0.2 ml), and dioxane (4 ml) was refluxed for 1.5 hr. Working up in the usual manner yielded **80** (17 mg) the identity of this sample was confirmed by IR spectral comparison.

7-Ethoxycarbonyl-3,6-dimethyl-4-oxo-3,4-dihydro-5*H*-pyrrolo[3,2-*d*]pyrimidine (80)——A mixture of **74** (250 mg) and 99% formic acid was refluxed for 3 hr. After evaporation of the solvent, the residue was mixed with benzene (10 ml). The insoluble crystals were collected and washed with benzene and then with AcOEt to obtain 80, yield 240 mg. Recrystallization from $CHCl_3$–methanol gave **80**, mp 288°. *Anal.* Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 55.90; H, 5.60; N, 17.73. UV λ_{max}^{EtOH} nm (ε): 234.5 (50500), 256 (shoulder, 8400). NMR (CF_3CO_2D): 1.53 (3H, t), 2.87 (3H, s), 3.99 (3H, s), 4.58 (2H, q), 9.27 (1H, s).

7-Ethoxycarbonyl-2,3,6-trimethyl-4-oxo-3,4-dihydro-5*H*-pyrrolo[3,2-*d*]pyrimidine (81)——a) A mixture of **76** (60 mg) and NaOEt (prepared from 100 mg of sodium) in ethanol (5 ml) was warmed at 50° for 1.5 hr. After dilution with water, the mixture was adjusted to pH 4.5 with aq. HCl and concentrated. The insoluble crystals were collected and washed with water; yield 55 mg. Recrystallization from ethanol gave **81**, colorless plates of mp 270° (30 mg). *Anal.* Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.86; H, 5.82; N, 16.68. UV λ_{max}^{EtOH} nm: 235.5. NMR (CF_3CO_2D): 1.55 (3H, t), 2.87 (3H, s), 3.18 (3H, s), 3.94 (3H, s), 4.60 (2H, q).

b) A mixture of **74** (230 mg), 2,4-pentanedione (150 mg), ethanol (8 ml), and HCl (0.1 ml) was heated at 100° for 2 hr. The reaction mixture was concentrated and the residue was diluted with water. The precipitated crystals were collected and washed with water to obtain **81** (yield 200 mg), which was recrystallized from ethanol, and identified with the product obtained by the above method a).

7-Ethoxycarbonyl-3,6-dimethyl-4-oxo-3,4-dihydro-5*H*-pyrrolo[3,2-*e*]-*v*-triazine (82)——A suspension of **74** (230 mg) in 4 N HCl (10 ml) was treated with $NaNO_2$ (90 mg) under ice-cooling. After 30 min, the mixture was allowed to stand at room temperature for 3 hr. The crystalline product **82** obtained by the usual work-up was recrystallized from DMF–ethanol to colorless plates of mp 242—244°. *Anal.* Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.94; H, 5.12; N, 23.66.

4-Ethoxycarbonyl-5-methyl-3-phenylureidopyrrole (83)——A mixture of phenyl isocyanate (6 ml) and **44** (5.5 g) in dry CH_3CN was refluxed for 1.5 hr. After removal of the solvent *in vacuo*, the residual crystals were collected and washed with AcOEt (6.5 g). Recrystallization from AcOEt–methanol gave **83** as colorless plates, mp 232—234°. *Anal.* Calcd. for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 62.11; H, 6.48; N, 10.59.

3-Butylureido-4-ethoxycarbonyl-5-methylpyrrole (84)——A mixture of butyl isocyanate (1 ml), **44** (1.0 g), and dry CH_3CN (20 ml) was refluxed for 8 hr. The solvent was removed *in vacuo* and the resulting precipitate was collected and washed with AcOEt (yield 1.0 g, 73%). Recrystallization from CH_2Cl_2–AcOEt gave **84** as colorless prisms of mp 192—194°. *Anal.* Calcd. for $C_{18}H_{29}N_3O_5$: C, 58.83; H, 7.96; N, 11.44. Found: C, 59.06; H, 8.10; N, 11.58.

7-*tert*-Butoxycarbonyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1*H*,6*H*-pyrrolo[3,4-*d*]pyrimidine (85)—— The 3-phenylureidopyrrole (**83**, 1.5 g) was stirred with NaOEt (prepared from 250 mg of sodium) in ethanol (25 ml) at room temperature for 30 min. The reaction mixture was concentrated *in vacuo*, acidified with dil. HCl to pH 3.5—4.0, and extracted with AcOEt. The organic layer was washed with water and dried. Evaporation of the solvent left crystalline **85**. Recrystallization from benzene–hexane gave colorless plates (1.2 g, 88%). An analytical sample was obtained by recrystallization from aq. ethanol; mp 158—159°. *Anal.* Calcd. for $C_{18}H_{19}N_3O_4 \cdot 1/2H_2O$: C, 61.71; H, 5.75; N, 11.99. Found: C, 62.01; H, 5.85; N, 11.71. MS *m/e*: 341 (M^+), 285, 268, 267, 241, 197, 175, 166, 149, 148, 122, 78. IR ν_{max}^{KBr} cm^{-1}: 3450, 3300, 1730, 1695 (shoulder), 1675, 1630, 1605 (shoulder). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435, 3255, 1725, 1678, 1630, 1600, 1545. NMR (DMSO-d_6): 1.57 (9H, s), 2.45 (3H, s), 7.1—7.4 (5H, m), 9.16 (1H, broad s), 12.20 (1H, broad s).

3-Butyl-7-*tert*-butoxycarbonyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1*H*,6*H*-pyrrolo[3,4-*d*]pyrimidine (86)——A solution of compound **84** (2.5 g) and NaOEt (prepared from 500 mg of sodium) in ethanol (60 ml) was stirred at room temperature. The reaction mixture was diluted with water and acidified with dil. HCl to pH 3; the resulting crystals were collected and washed with water to obtain **86** (2.0 g, 91%), which was recrystallized from CH_2Cl_2–hexane to colorless plates of mp 194—196°. *Anal.* Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21; N, 13.08. Found: C, 59.89; H, 7.20; N, 13.02. UV λ_{max}^{EtOH} nm (ε): 240 (32000), 271 (17800).

IR ν_{max}^{Nujol} cm^{-1}: 3420, 3220, 1720, 1650, 1620. NMR (DMSO-d_6): 0.91 (3H, t), 1.1—1.6 (4H, m), 1.56 (9H, s), 2.47 (3H, s), 3.81 (2H, q), 9.00 (1H, s), 12.11 (1H, broad s).

7-*tert*-Butoxycarbonyl-5,6-dimethyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine (87)——a) Me_2SO_4 (3 ml) was added dropwise at 0° to a mixture of anhyd. K_2CO_3 (10 g), **85** (5 g), and DMSO (40 ml). The mixture was then stirred for 40 min at room temperature and diluted with ice-water. The resulting precipitate was collected and recrystallized from $CHCl_3$–ethanol to obtain **87** (2.8 g), mp 308—310° (turned to needles at *ca.* 260°). *Anal.* Calcd. for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.04; H, 5.73; N, 11.88. MS *m/e*: 355 (M^+), 299, 282, 281, 256, 255, 253, 211, 207, 180, 163, 136 (base peak), 119, 107, 91, 77, 67, 57, 56. IR ν_{max}^{KBr} cm^{-1}: 3450, 1715, 1685, 1660, 1620, 1600 (shoulder), 1590(shoulder), 1550, 1515, 1500. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3448, 1724 (shoulder), 1695, 1670, 1626, 1603, 1538, 1515, 1499. NMR ($CDCl_3$): 1.62 (9H, s), 2.55 (3H, s), 3.81 (3H, s), 7.1—7.4 (5H, m), 8.48 (1H, s). The mother liquor of the first crop of **87** was concentrated to deposit **88** (500 mg).

b) A mixture of the aminopyrrole (**44**, 1.1 g), anhyd. K_2CO_3 (2.5 g), and DMSO (30 ml) was stirred at room temperature. To the mixture was added a solution of methyl iodide (0.3 ml) in DMSO (3 ml) in three portions. After stirring for further 2 hr, the mixture was diluted with ice-water and extracted with CH_2Cl_2. Evaporation of the CH_2Cl_2 left a yellow oil of mono-N-methyl compound, **89** (1.2 g), which crystallized upon standing. Recrystallization from Et_2O–hexane gave pure N-methyl derivative (**89**), mp 85°. *Anal.* Calcd. for $C_{14}H_{22}N_2O_4$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.66; H, 8.04; N, 9.79. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3470, 1685, 1650. The compound **89** was treated with phenyl isocyanate and the product was then cyclized to **87** with NaOEt in the same manner as that of the reactions (**44**→**83**→**85**).

7-*tert*-Butoxycarbonyl-1,5,6-trimethyl-2,4-dioxo-3-phenylpyrrolo[3,4-*d*]pyrimidine (88)——To a mixture of **87** (1.5 g), anhyd. K_2CO_3 (3 g), and DMF (80 ml) was added Me_2SO_4 (2 ml) dropwise. After stirring for 3.5 hr at room temperature, the reaction mixture was diluted with ice-water. The resulting precipitate was collected and washed with water to obtain crystalline **88** (1.5 g). Recrystallization from ethanol gave colorless prisms, mp 230—231°. *Anal.* Calcd. for $C_{20}H_{23}N_3O_4$: C, 65.02; H, 6.28; N, 11.38. Found: C, 65.00; H, 6.33; N, 11.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1709, 1695, 1667, 1605 (shoulder), 1595, 1499. NMR ($CDCl_3$): 1.60 (9H, s), 2.57 (3H, s), 3.55 (3H, s), 3.67 (3H, s), 7.1—7.4 (5H, m).

5,6-Dimethyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine (90)——A solution of **87** (700 mg) in trifluoroacetic acid (10 ml) was stirred for 2.5 hr at room temperature. After addition of ice-water, the resulting precipitate was collected and washed with water. Recrystallization from acetone gave **90** (300 mg, 60%) as colorless plates, mp 305—308° (turned to needles at *ca.* 260°). MS *m/e*: 255 (M^+), 163, 136 (base peak), 107, 91, 67. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1720, 1660. NMR ($CDCl_3$): 2.54 (3H, s), 3.50 (3H, s), 6.02 (1H, s), 7.1—7.4 (5H, m), 8.82 (1H, broad s).

1,5,6-Trimethyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydropyrrolo[3,4-*d*]pyrimidine (91)——Compound **91** (1.6 g, 99.8%) was similarly obtained by the reaction of **88** (2.2 g) and trifluoroacetic acid as described above. Recrystallization from acetone gave **91** as colorless plates, mp 236—238°. *Anal.* Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.95; H, 5.43; N, 15.77. MS *m/e*: 269 (M^+), 149, 121, 28 (base peak). IR ν_{max}^{KBr} cm^{-1}: 1700, 1655, 1615, 1600, 1545. NMR ($CDCl_3$): 2.54 (3H, s), 3.32 (3H, s), 3.54 (3H, s), 6.19 (1H, s), 7.1—7.4 (5H, m).

3-Benzyl-1,5,6-trimethyl-7-dimethylaminomethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,4-*d*]pyrimidine (92)——A mixture of **91** (0.6 g), 37% formalin (0.8 ml), dimethylamine hydrochloride (0.7 g), AcONa (0.7 g), and AcOH (20 ml) was stirred at room temperature for 5.5 hr. After evaporation of the AcOH, the residue was made alkaline (pH 13) with aq. 40% KOH solution. The precipitate was collected and dissolved in AcOEt. The AcOEt solution was absorbed on a column of Al_2O_3 (Wako Pure Chemical, 25 g). Elution of the column with benzene–acetone (10: 1) afforded colorless crystals of **92**; yield 100 mg (17%). Recrystallization from benzene–hexane gave prisms, mp 183—185°. MS *m/e*: 326 (M^+), 282, 163. UV λ_{max}^{EtOH} nm (ε): 227 (30100), 254 (8500), 290 (2800). IR ν_{max}^{Nujol} cm^{-1}: 1700, 1650, 1613. NMR ($CDCl_3$): 2.24 (6H, s), 2.56 (3H, s), 3.56 (5H, overlapped s), 3.61 (3H, s), 7.1—7.4 (5H).

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