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3-Hydroxypyrroles. II.[1] The Reaction of 4,5-Unsubstituted Alkyl 3-Hydroxypyrrole-2-carboxylates with Some Electrophiles[2]

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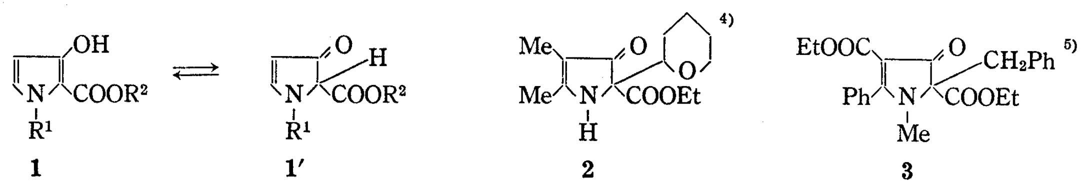
The reaction of alkyl 3-hydroxypyrrole-2-carboxylates (**1**) with some electrophiles was investigated. The alkylation of **1c** occurred at the O and C-2 position as in the case of usual β-keto esters. An N-substituted 3-hydroxypyrrole-2-carboxylate (**1e**) reacted at the 2-position upon the Michael reaction. In addition to the C-2 adduct (**9**), an unexpected 2,2-bis-adduct (**10**) was concurrently obtained possibly *via* the ketonic cleavage of the mono-adduct (**9**) followed by the second addition of acrylate. The N-unsubstituted one (**1b**) gave a mono-adduct at C-2 (**12**) and a bis-adduct at C-2 and N (**13**). Upon bromination, **1c** reacted at the 4- and 5-position, not at the 2-position; namely **1c** reacted with bromine as an enamine or a pyrrole, and not as a β-keto ester. The Mannich reaction occurred rapidly and selectively at the 4-position, and the 4-bromo derivative (**15**) reacted preferentially at the 5-position. In the cyanation of the quarternary salts of the Mannich bases, a dimer (**23**), a trimer (**24**) and a dicyano compound (**26**) were obtained in addition to the expected cyanides (**22**, **25**).

Keywords——3-hydroxypyrrole-2-carboxylates; 4-oxo-2-pyrrolines; competitive C- and O-alkylation; Claisen rearrangement; Michael reaction; bromination; Mannich reaction; cyanide replacement of pyrrolic ring bromide

In the previous paper,[1] we reported the synthesis of 4,5-unsubstituted alkyl 3-hydroxypyrrole-2-carboxylates (**1**). They are expected to possess both the pyrrole or enamine type and pyrrolinone or enolized α-ketonic reactivities. The latter reactivity has been detected in the tetrahydropyranylation of ethyl 4,5-dimethyl-3-hydroxypyrrole-2-carboxylate[4] (see **2**) or in the benzylation of the sodium salt of diethyl 1-methyl-5-phenyl-3-hydroxypyrrole-2,4-dicarboxylate[5] (see **3**) (Chart 1).



	R¹	R²		R¹	R²
a :	H	Et	**e** :	PhCH₂	Et
b :	H	*t*-Bu	**f** :	PhCH₂	*t*-Bu
c :	Me	Et	**g** :	Ph	Et
d :	Me	*t*-Bu	**h** :	Ph	*t*-Bu

Chart 1

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1) Part I: T. Momose, T. Tanaka, T. Yokota, N. Nagamoto, and K. Yamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 2224 (1978).
2) A preliminary communication of this work has appeared in part in *Heterocycles*, **6**, 1821 (1977).
3) Location: *133-1, Yamada-kami, Suita, Osaka 565, Japan.*
4) R. Chong and P.S. Clezy, *Aust. J. Chem.*, **20**, 935 (1967).
5) E. Campaigne and G.M. Shutske, *J. Heterocycl. Chem.*, **11**, 929 (1974).

However, no systematic studies on the reactivities associated with the tautomerism of the 3-hydroxypyrrole system have been described.6)

We have investigated the reactivity of **1** as a β-keto ester by examining the reaction with some electrophiles in order to explore preliminarily its utility as a synthon for azacyclic molecules.

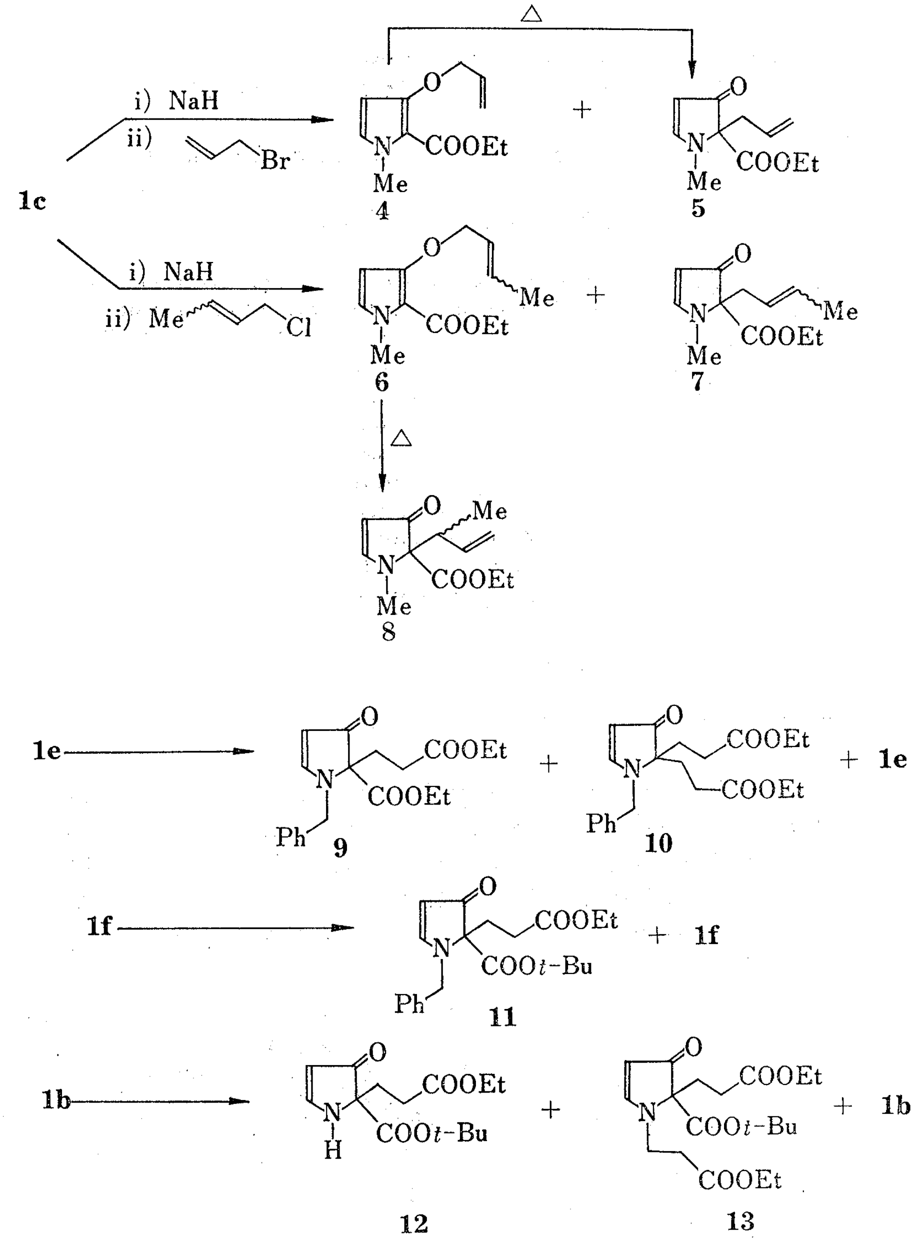

Chart 2

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6) The chemistry of 3-hydroxypyrrole derivatives has been investigated in association with their reactivity, especially toward alkylation and oxidation as in the methylation with diazomethane[a–c] or dimethyl sulfate,[4,c,d] in the acylation[c] or chlorination[e] at the hydroxyl, and in the oxidation[5,g–m] or the condensation with aromatic aldehydes[f,k] at the 2-position: *a*) J. Davoll, *J. Chem. Soc.*, **1953**, 3802; *b*) H. Rapoport and K.G. Holden, *J. Am. Chem. Soc.*, **84**, 635 (1962); *c*) M. Friedman, *J. Org. Chem.*, 30, 859 (1965); *d*) E. Benary and R. Konrad, *Ber.*, **56B**, 44 (1923); *e*) N. Yoshida, *Yakugaku Zasshi*, **86**, 158 (1966); *f*) H. Bauer, *Chem. Ber.*, **104**, 259 (1971); *g*) R. Kuhn and G. Osswald, *ibid.*, **89**, 1423 (1956); *h*) A. Treibs and A. Ohorodnik, *Ann.*, **611**, 149 (1958); *i*) R.S. Atkinson and E. Bullock, *Can. J. Chem.*, **42**, 1524 (1964); *j*) H. Bauer, *Chem. Ber.*, **100**, 1704 (1967); *k*) H. Bauer, *Angew. Chem.*, **80**, 758 (1968); *l*) H. Bauer, *Chem. Ber.*, **101**, 1286 (1968); *m*) H. Bauer, *Ann.*, **736**, 1 (1970).

1. Alkylation

Earlier works describing the alkylation of 3-hydroxypyrrole derivatives were concerned only with the procedure to protect their hydroxyl group.[6a-c] We have examined the alkylation of the sodium salt of the 3-hydroxypyrrole-2-carboxylate (**1c**) with allyl bromide in hopes of introduction of the functionalized carbon chain into this molecule at C-2 (Chart 2).

Two products were obtained: one was a normal allyl ether (**4**) (32%), and the other a pyrrolinone derivative (**5**) (62%). The ultraviolet (UV) spectrum of **5** displayed the absorption maximum characteristic of the pyrrolinone system[6a] at 332 nm (ε=7600), and the proton magnetic resonance (PMR) signals for two olefinic ring protons appeared with markedly large separation at δ 4.87 and 7.79 as doublets (J=3.5 Hz). The infrared (IR) spectrum (KCl) indicated the bands due to an aliphatic ester and a β-aminoenone at 1735 and 1642 cm^{-1}, respectively. The O-alkylated product (**4**) was easily converted to **5** by its heating at 180—200°, but this Claisen rearrangement did not occur at the alkylation temperature (70—80°) in benzene. Consequently, in this alkylation, O- and C-alkylation were found to proceed concurrently. This mode of alkylation was confirmed by the alkylation with crotyl chloride instead of allyl bromide. The C-alkylated product (**7**) was not identical with the rearrangement product (**8**) obtained by heating the O-alkylated one (**6**). The rearrangement product (**8**) was a mixture of diastereoisomers in the ratio of *ca.* 5:4 on inspection of the PMR spectrum,[7] but no attempts were made to separate them. The formation of these diastereoisomers seems to result from the mixed geometry of commercial crotyl chloride.

2. The Michael Reaction

There has been found a few reports on the Michael reaction of pyrroles: N-adducts result by use of basic catalysts;[8] C-adducts by use of[9] or without[10] acidic catalysts.

We have examined the Michael reaction of **1** with ethyl acrylate by use of Triton B as a catalyst in order to confirm their nature as a β-keto ester (Chart 2).

The reaction of **1e** with 1.5 molar equivalents of ethyl acrylate gave an expected adduct (**9**) in 29% yield and an unexpected bis-adduct (**10**) in 7% yield with recovery of the starting material. The bis-adduct (**10**) would be generated from the ketonic cleavage of **9** under the basic reaction condition followed by the second addition of another ethyl acrylate, since the isolated mono-adduct (**9**) was easily converted into **10** in the presence of ethyl acrylate under the same reaction condition. When R^2 was *t*-butyl (**1f**), only the mono-adduct (**11**) was obtained owing to inaccessibility of hydroxide ion to its *t*-butoxycarbonyl to be cleaved. On the other hand, a 4-ethoxycarbonyl analogue of **1f** gave mono- and bis-adduct in this reaction (see Experimental). The reaction of the N-hydrogen derivative (**1b**) with 2.5 molar equivalents of ethyl acrylate gave the C-2 adduct (**12**) and the C-2, N bis-adduct (**13**) in 32% and 52% yield, respectively.

In brief, the 3-hydroxypyrrole-2-carboxylates (**1**) clearly have a β-keto ester-like character[11] as evidenced by their behavior toward alkylation and the Michael reaction, and their C-2 position is moderately reactive enough to accept functionalized homologations. The 4-oxo-2-pyrroline derivatives (**5**, **7**, **8** and **9**—**13**) obtained in this study are the first instances

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[7] The terminal methyl of **6** or **7** appeared at δ 1.72 or 1.60 as a doublet-like signal closely resembled that of commercial crotyl chloride, but the methyl signal of **8** appeared as two doublets at δ 0.87 (J=6.4 Hz) and 1.17 (J=7.6 Hz), respectively.

[8] H. Fischer and H. Loewe, *Ann.*, **615**, 124 (1958); J.T. Braunholtz, K.B. Mallion, and F.G. Mann, *J. Chem. Soc.*, **1962**, 4346; V. Carelli, M. Cardellini, and F. Morlacchi, *Ann. Chim.* (Rome), **53**, 309 (1963); T. Murata, T. Sugawara, and K. Ukawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 2571 (1973).

[9] A. Treibs and K-H. Michl, *Ann.*, **589**, 163 (1954); A. Treibs and E. Herrmann, *Ann.*, **592**, 1 (1955); I.D. Webb and G.T. Borcherdt, *J. Am. Chem. Soc.*, **73**, 752 (1951).

[10] D.O. Cheng, T.L. Bowman, and E. LeGoff, *J. Heterocycl. Chem.*, **13**, 1145 (1976).

[11] This character has also been observed in the cleavage of ethyl 4,5-dimethyl-3-hydroxypyrrole-2-carboxylate with boiling 6 N hydrochloric acid: see G. Pfeiffer and H. Bauer, *Ann.*, **1976**, 383.

of 2,3- or 1,2,3-unsubstituted 4-oxo-2-pyrrolines. The comparison of the spectral properties of the enaminoketone moiety in **12** with those of 4-oxo-1,2,3,4-tetrahydropyridine[12] (**14**) is of interest: IR carbonyl bands (cm^{-1}): 1650 (KCl) for **12** and 1620 (film) for **14**; UV absorptions (nm): 318 (ε=7000) in ethanol for **12** and 313 (ε=18400) in methanol for **14**; PMR chemical shifts for olefinic protons δ ($CDCl_3$): 5.18 (d), 8.12 (t) for **12** and 4.99 (d), 7.26 (t) for **14**; the coupling constants (J): 3.6 Hz for **12** and 7 Hz for **14**.

3. Bromination

Selective halogenation of pyrrolic compounds is generally difficult. There are no reports describing the halogenation of 3-hydroxypyrrole derivatives, probably because of unavailability of the compounds nonsubstituted at the ring carbon. Pyrroles having a carbonyl group at the 2-position react with halogen mainly at the 4-position.[13,14] Meanwhile, β-keto esters can react with halogen at the enolizable α-ketonic carbon[15] as evidenced by the bromination of a malonic ester[16] or a tetralone ester.[17] If the 3-hydroxypyrrole-2-carboxylates (**1**) react with bromine as the vinylogous lactam (**1′**), they have two possible reactive centers: the 4-position (as enamines)[18,19] and the 2-position (as active methyne).

From the above viewpoints, we have investigated the bromination of **1c** as one of the examinations of their reactivity toward electrophiles (Chart 3).

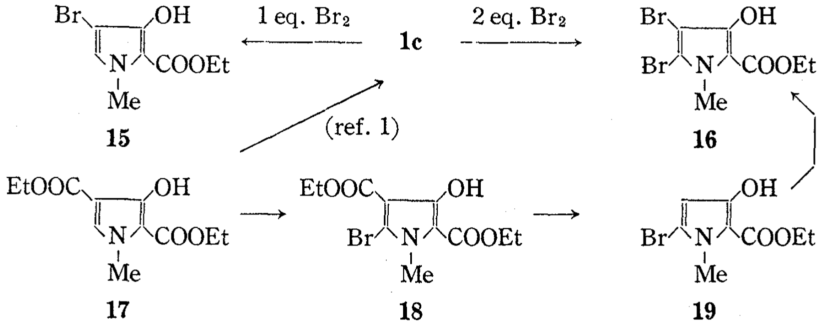

Chart 3

Slow addition of a dilute chloroform solution of one molar equivalent of bromine to a solution of **1c** gave a monobromide (**15**). A dibromide (**16**) was obtained by treating **1c** with 2 molar equivalents of bromine, and no bromination at the C-2 was detected. On the other hand, bromination of a diester (**17**) gave the bromodiester (**18**), which was hydrolyzed and decarboxylated to give the 5-bromo-3-hydroxypyrrole-2-carboxylate (**19**). The bromides **15, 16, 18** and **19** were positive on the ferric chloride test, and the PMR signal of the ring proton in the monobromide (**15**) appeared at δ 6.49 while that in **19** at δ 5.80. Consequently, this system reacts with bromine as a pyrrole or enamines, and not as a keto ester. Furthermore, the preparation of regioisomers such as **15** and **19** by altering the bromination step in the synthetic path demonstrates synthetic utility of the bromination of this system as

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12) A. Haider, G. Cornuz, and H. Wyler, *Helv. Chim. Acta*, **58**, 1287 (1975).
13) G.R. Birchall and A.H. Rees, *Can. J. Chem.*, **49**, 919 (1971).
14) C. Jaureguiberry, M.C. Fournie-Zaluski, J.P. Chevallier, and B. Roques, *C. R. Acad. Sci. Ser. C*, **273**, 276 (1971).
15) In the case of ethyl acetoacetate, the bromination is not straightforward: α or γ bromination can occur depending on reaction conditions; *e.g.*, R.M. Dodson, E.R. Peterson, and J.K. Seyler, *J. Am. Chem. Soc.*, **72**, 3281 (1950).
16) C.S. Palmer and P.W. McWherter, "Organic Syntheses," Coll. Vol. I, ed. by H. Gilman and A.H. Blatt, John Wiley and Sons, Inc., New York, 1945, p. 245.
17) Z. Horii, T. Katagi, Y. Tamura, and T. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **10**, 887 (1962).
18) G.H. Alt, "Enamines," ed. by A.G. Cook, Marcel Dekker, New York, 1969, p. 154.
19) I. Jirkovsky, *Can. J. Chem.*, **52**, 55 (1974).

preliminary or 'dummy' functionalization which controls the mode of substitution by activating or blocking at C-4 or 5 and enables the subsequent modification at this position to be selective.

4. The Mannich Reaction

It is known that the quarternary salts of the Mannich base from pyrroles are useful as alkylating agents.[20] It is also of interest whether **1** reacts as an enamine at the olefinic carbon (*e.g.*, as in the case of antipyrine) or as a β-keto ester at the active methyne.[21] We have examined the reactivity of **1c** toward the Mannich reaction as one of the exploratory experiments associated with synthetic designs (Chart 4).

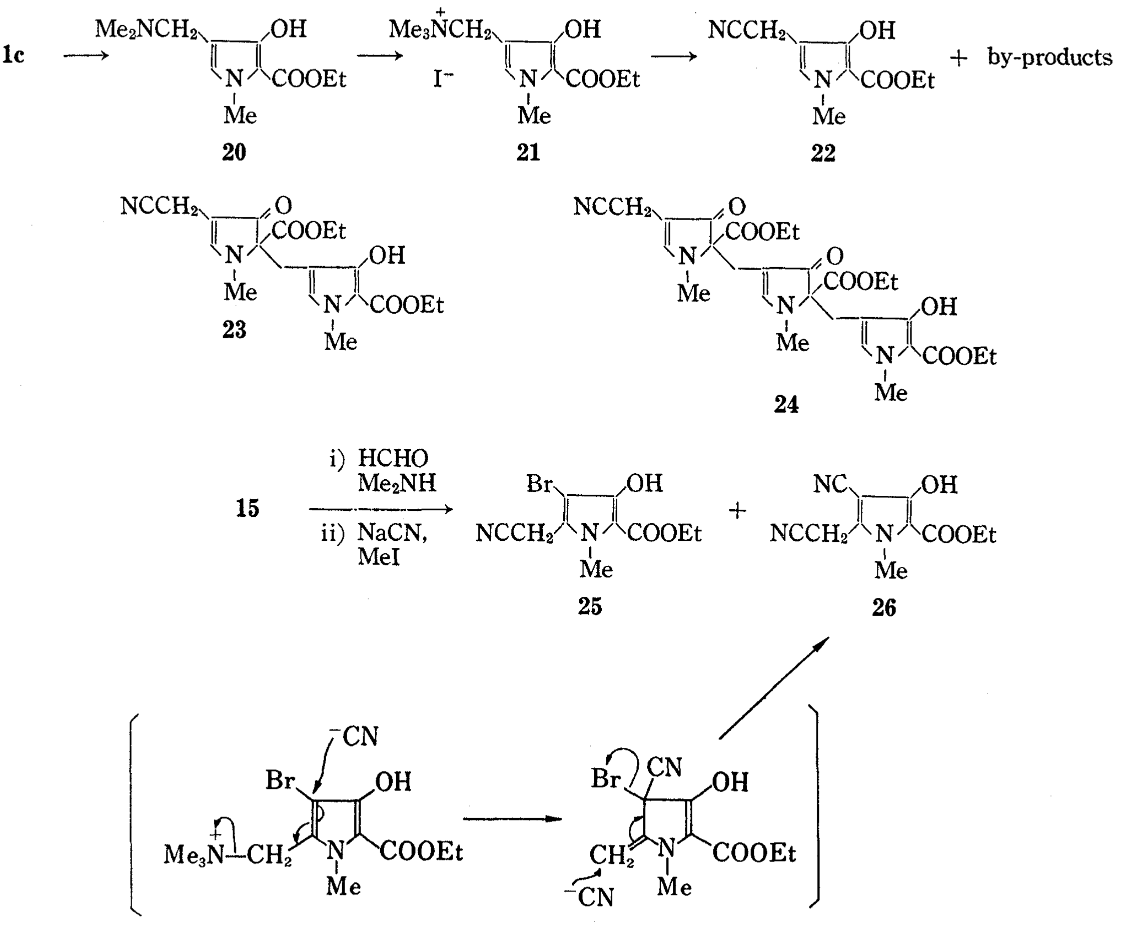

Chart 4

Ethyl 4-dimethylaminomethyl-1-methyl-3-hydroxypyrrole-2-carboxylate (**20**) was obtained in quantitative yield by treating **1c** with dimethylamine and formalin. The aminoalkylation at C-2 failed to be detected on repeated experiments. The Mannich base (**20**) was converted to the 4-cyanomethyl-3-hydroxypyrrole-2-carboxylate (**22**) *via* the quarternary salt (**21**) in 12% yield. The low yield of **22** was due to the formation of by-products. One of the by-products was positive on a ferric chloride test and showed absorption maxima at 267 nm

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20) N.J. Leonard and E.H. Burk, Jr., *J. Am. Chem. Soc.*, **72**, 2543 (1950); W. Herz and J.L. Rogers, *ibid.*, **73**, 4921 (1951); A. Treibs and W. Ott, *Ann.*, **615**, 137 (1958); W. Herz and R.L. Settine, *J. Org. Chem.*, **24**, 201 (1959); S. Umino, K. Kariyone, K. Tanaka, and I. Ueda, *Chem. Pharm. Bull.* (Tokyo), **17**, 605 (1969).

21) Both types are known to be reactive toward the Mannich reaction: see F.F. Blicke, "Organic Reactions," Vol. 1, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1942, p. 303.

(ε=18600) and 338 nm (ε=7400) in its UV spectrum, the former being due to the 3-hydroxypyrrole-2-carboxylate and the latter to the 4-oxo-2-pyrroline system contained in the molecule. The IR spectrum ($CHCl_3$) of this compound indicated a hydroxyl at 3480, a nitrile at 2240, an aliphatic ester at 1730, a pyrrolic ester[1)] at 1702, a pyrrolinone at 1665, and an intramolecularly hydrogen-bonded pyrrolic ester[1)] at 1643 cm^{-1}. In its PMR spectrum, the signal for an N-methyl of pyrrolinone appeared at δ 3.21, an N-methyl of pyrrole at 3.63, a pyrrolic ring proton at 6.30, and an olefinic ring proton of pyrrolinone at 7.72, and its molecular ion peak appeared at m/e: 389 (6.8%) in the mass (MS) spectrum. From the above data, this compound is presumed to have the pyrrolinylmethylpyrrole structure (**23**) probably derived from the reaction of **22** with **21**. The other by-product (**24**) was also isolated.[22)]

On the other hand, the Mannich reaction of the 4-bromo derivative (**15**) followed by quaternization and subsequent cyanation gave complex products. The only products isolated were the normal 5-cyanomethyl derivative (**25**) (3.0% yield) and a dicyano compound (**26**) (30.1% yield). Attempted cyanation of **25** into **26** under a similar condition resulted in complete recovery of **25**. Compound **26** was possibly derived from dual vinylogous cyanation of the quaternary salt (Chart 4). The Mannich reaction at the C-4 position of this system (**20**) came to completion within one hour, but the reaction at the C-5 position in **15** was slow and accompanied by formation of unidentified side products. The difference of the reactivity between the C-4 and C-5 position would result from the effect of an electron-withdrawing ester group at the 2-position. Consequently, this system was found to react toward Mannich reagents as a pyrrole, not as a ketone.[23)]

As a summary, the introduction of a side chain on the 2-position was made possible by the alkylation or the Michael reaction, and that on the 4- and 5-position by Mannich reaction. Therefore, we could suggest the possible utility of **1** as a synthetic intermediate capable of the regioselective introduction of a carbon chain bearing various functionalities. In addition, it has become apparent that the reaction center of the 3-hydroxypyrrole-2-carboxylate (**1**) varies depending on the softness[24)] of electrophiles. It seems likely that the 2-position of **1** reacts with softer acids, *e.g.*, ethyl acrylate, while the 4- and 5-position react with harder acids, *e.g.*, Mannich reagents.

Experimental[25)]

Allylation of Ethyl 1-Methyl-3-hydroxypyrrole-2-carboxylate (1c)——A solution of **1c** (0.5 g) in dry benzene (10 ml) was added to a stirred suspension of NaH (0.2 g) and dry benzene (20 ml), and followed by heating at 60—70° for 1 hr. To the resulting suspension was added a solution of allyl bromide (2.6 ml) in dry benzene (20 ml), and followed by heating at 70—80° for 6 hr with stirring. After being cooled, and

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22) Recently, an abnormal displacement in the reaction of the quaternary salts of a pyrrole Mannich base was observed by Carson *et al.*: J.R. Carson, J.T. Hortenstine, B.E. Maryanoff, and A.J. Molinari, *J. Org. Chem.*, **42**, 1096 (1977).

23) In the Mannich reaction of the 4-substituted derivative (**15**), the aminomethylation at the C-2 position may have occurred to a slight extent, because a small amount of non-enolic products was detected on thin-layer chromatography (TLC). The extract of the TLC zone of a high *Rf* value [*ca.* 0.7 on alumina in chroroform–ethanol (10:1)] was negative on ferric chloride test, displayed the signal of an olefinic proton at δ 8.00 and of dimethylaminomethyl at 2.45 in the PMR spectrum, and showed absorption maximum at 327 nm in the UV spectrum, the feature being characteristic of the pyrrolinone system. The aminomethylated product, however, failed to be isolated in pure form owing to its instability.

24) *cf.* R.G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963); *idem*, *Science*, **151**, 172 (1966); M. Tanaka, K. Morita, and K. Saito, *Kagaku To Kogyo*, 26, 184 (1973); T–L. Ho, *Chem. Rev.* **75**, 1 (1975).

25) All melting points are uncorrected. IR, MS, UV and PMR spectra were recorded on Hitachi EPI–G3, Hitachi RMU–6E, Hitachi 124 Spectrophotometer and Hitachi R–20A or R–22, respectively. In the PMR spectra, tetramethylsilane was used as an internal standard, and coupling constants (*J*) are given in Hz. All the organic extracts were washed with satd. NaCl solution and dried over anhydrous magnesium sulfate before evaporation. Preparative thin-layer chromatography (PLC) was performed on Merck Kieselgel 60 PF_{254}.

filtered, the filtrate was concentrated and purified by PLC (benzene: EtOH=10: 1) to give two products: one was ethyl 3-allyloxy-1-methylpyrrole-2-carboxylate (**4**) [0.2 g (32.2%), colorless oil], and the other was ethyl 5-allyl-1-methyl-4-oxo-2-pyrroline-5-carboxylate (**5**) (0.39 g, 63.1%) as colorless needles (from cyclohexane), mp 45.0—47.0°. Compound **4** gave **5** in almost quantitative yield upon heating at 180—200° for 5 min. Compound **4**: IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1680, 1535. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 267 (11200). PMR ($\mathrm{CCl_4}$) δ: 1.38 (3H, t, J=6.6), 3.82 (3H, s), 4.24 (2H, q, J=6.6), 4.36—4.50 (2H, m, $\mathrm{OC\underline{H}_2{-}CH{=}}$), 4.96—5.97 (3H, m, $\mathrm{CH_2{-}C\underline{H}{=}C\underline{H}_2}$), 5.64 (1H, d, J=3.0, $\mathrm{C_4}$–H), 6.48 (1H, d, J=3.0, $\mathrm{C_5}$–H). Compound **5**: IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 1735, 1642. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 332 (7600). MS *m/e*: 209 (M$^+$, 7.0%), 28 (100%). PMR ($\mathrm{CCl_4}$) δ: 1.29 (3H, t, J=6.6), 1.90—2.95 (2H, m, $\mathrm{C\underline{H}_2{-}CH{=}}$), 3.03 (3H, s), 4.18 (2H, q, J=6.6), 4.87 (1H, d, J=3.5, $\mathrm{C_3}$–H), 4.90—5.40 (3H, m, $\mathrm{CH_2{-}C\underline{H}{=}C\underline{H}_2}$), 7.79 (1H, d, J=3.5, $\mathrm{C_2}$–H). *Anal.* Calcd. for $\mathrm{C_{11}H_{15}NO_3}$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.23; H, 7.23; N, 6.40.

2-Butenylation of Ethyl 1-Methyl-3-hydroxypyrrole-2-carboxylate (1c)——The reaction was performed in the same manner as the allylation of **1c**: **1c**, 0.3 g; NaH, 60 mg; crotyl chloride, 1.6 g. The crude product was purified by PLC (benzene: EtOH=10: 1) to give ethyl 3-(2-butenyloxy)-1-methylpyrrole-2-carboxylate (**6**) (0.28 g, 70.7%, a mixture of geometric isomers) as a colorless oil and ethyl 5-(2-butenyl)-1-methyl-4-oxo-2-pyrroline-5-carboxylate (**7**) (95 mg, 24.0%, a mixture of geometric isomers) as a colorless oil. Compound **6**: IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1690, 1540. MS *m/e*: 223 (M$^+$, 16.0%), 122 (100%). PMR ($\mathrm{CCl_4}$) δ: 1.31 (3H, t, J=7.0), 1.72 (3H, d-like, $\mathrm{CH{=}CH{-}C\underline{H}_3}$), 3.50—4.50 (2H, m, $\mathrm{OC\underline{H}_2{-}CH{=}}$), 3.79 (3H, s), 4.20 (2H, q, J=7.0), 5.20—6.00 (2H, m, –CH=CH–), 5.57 (1H, d, J=3.0, $\mathrm{C_4}$–H), 6.39 (1H, d, J=3.0, $\mathrm{C_5}$–H). Compound **7**: IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1750, 1735, 1684. MS *m/e*: 223 (M$^+$, 14.0%), 123 (100%). PMR ($\mathrm{CCl_4}$) δ: 1.25 (3H, t, J=7.0), 1.60 (3H, d-like), 2.1—3.2 (2H, m), 3.00 (3H, s), 4.13 (2H, q, J=7.0), 4.6—5.9 (2H, m), 4.82 (1H, d, J=3.4, $\mathrm{C_3}$–H), 7.70 (1H, d, J=3.4, $\mathrm{C_2}$–H).

Ethyl 5-Methallyl-1-methyl-4-oxo-2-pyrroline-5-carboxylate (8)——Compound **6** (100 mg) was heated at 170—180° for 20 min, and the product was purified by PLC (benzene: EtOH=10: 1) to give **8** (58 mg, a mixture of geometric isomers) with recovery of the starting material **6** (22 mg). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1725, 1675. MS *m/e*: 223 (M$^+$, 20.0%), 123 (100%). PMR ($\mathrm{CCl_4}$) δ: 0.87 (d, J=6.4), 1.17 (d, J=7.6), 1.29 (3H, t, J=7.0), 2.90—3.45 (m), 3.08 (s), 3.15 (s), 4.18 (2H, q, J=7.0), 4.80—4.82 (d, J=3.4), 4.84 (d, J=3.8), 7.69 (d, J=3.4), 7.76 (d, J=3.8).

The Michael Reaction of Ethyl 1-Benzyl-3-hydroxypyrrole-2-carboxylate (1e) with Ethyl Acrylate——A mixture of **1e** (120 mg), ethyl acrylate (0.08 ml), two drops of Triton B (40% methanol solution) and EtOH (10 ml) was refluxed for 3 hr. After addition of cold water (20 ml), the mixture was acidified with 10% $\mathrm{H_2SO_4}$, and extracted with $\mathrm{CHCl_3}$. The extract was washed with satd. $\mathrm{NaHCO_3}$, dried, and evaporated. The residue was purified by PLC (benzene: EtOH=10: 1) to give ethyl 1-benzyl-5-ethoxycarbonyl-4-oxo-2-pyrroline-5-propionate (**9**) (24 mg, 14.2%) as a colorless oil and diethyl 1-benzyl-4-oxo-2-pyrroline-5,5-dipropionate (**10**) (54 mg, 29.3%) as colorless needles (from benzene–cyclohexane), mp 115.0—116.0°, with recovery of the starting material (55 mg). Compound **9**: IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1740, 1690. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 332 (11100). MS *m/e*: 345 (M$^+$, 12.2%), 91 (100%). PMR ($\mathrm{CCl_4}$) δ: 1.36 (6H, t, J=7.6, $\mathrm{OCH_2C\underline{H}_3}\times 2$), 1.8—2.6 (4H, m, $\mathrm{{-}CH_2CH_2COO}$), 4.07 (2H, q, J=7.6), 4.09 (2H, q, J=7.6), 4.38 (2H, s, $\mathrm{{-}CH_2{-}Ph}$), 4.94 (1H, d, J=3.4, $\mathrm{C_3}$–H), 7.32 (5H, s, benzene ring H), 7.72 (1H, d, J=3.4, $\mathrm{C_2}$–H). *Anal.* Calcd. for $\mathrm{C_{19}H_{23}NO_5}$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.70; H, 6.75; N, 4.13. Compound **10**: IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 1735, 1646. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 327 (11900). MS *m/e*: 373 (M$^+$, 10.0%), 91 (100%). PMR ($\mathrm{CDCl_3}$) δ: 1.24 (6H, t, J=7.0, $\mathrm{OCH_2C\underline{H}_3}\times 2$), 2.09 (8H, s-like, $\mathrm{{-}CH_2CH_2COO}\times 2$), 4.12 (4H, q, J=7.0, $\mathrm{OC\underline{H}_2CH_3}\times 2$), 4.38 (2H, s, $\mathrm{CH_2{-}Ph}$), 5.12 (1H, d, J=3.4, $\mathrm{C_3}$–H), 7.35 (5H, s, benzene ring H), 7.74 (1H, d, J=3.4, $\mathrm{C_2}$–H). *Anal.* Calcd. for $\mathrm{C_{21}H_{27}NO_5}$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.61; H, 7.28; N, 3.89.

The Michael Reaction of *t*-Butyl 1-Benzyl-3-hydroxypyrrole-2-carboxylate (1f) with Ethyl Acrylate——A mixture of **1f** (100 mg), ethyl acrylate (0.06 ml), two drops of Triton B, and EtOH (10 ml) was refluxed for 5 hr. After the same work-up as in the case of **1e**, the product was purified by PLC (benzene: EtOH=10: 1) to give ethyl 1-benzyl-5-*t*-butoxycarbonyl-4-oxo-2-pyrroline-5-propionate (**11**) (70 mg, 51.2%) as a colorless oil with recovery of the starting material (33 mg). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1743, 1688. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 330 (11700). MS *m/e*: 373 (M$^+$, 3.9%), 91 (100%). PMR ($\mathrm{CCl_4}$) δ: 1.20 (3H, t, J=6.6), 1.42 (9H, s), 1.9—2.4 (4H, m, $\mathrm{{-}CH_2CH_2COO}$), 4.04 (2H, q, J=6.6), 4.31 (2H, s, $\mathrm{CH_2{-}Ph}$), 4.87 (1H, d, J=3.6, $\mathrm{C_3}$–H), 7.29 (5H, s), 7.53 (1H, d, J=3.6, $\mathrm{C_2}$–H). *Anal.* Calcd. for $\mathrm{C_{21}H_{27}NO_5 \cdot 1/4\ H_2O}$: C, 66.73; H, 7.34; N, 3.71. Found: C, 66.67; H, 7.29; N, 3.79.

The Michael Reaction of *t*-Butyl 1-Benzyl-4-ethoxycarbonyl-3-hydroxypyrrole-2-carboxylate with Ethyl Acrylate——A mixture of *t*-butyl 1-benzyl-4-ethoxycarbonyl-3-hydroxypyrrole-2-carboxylate (200 mg), ethyl acrylate (0.19 ml), two drops of Triton B and EtOH (15 ml) was refluxed for 5 hr. After the same work-up as in the case of **1e**, the product was purified by PLC (benzene: EtOH=100: 15). The fraction of higher *Rf* value gave ethyl 1-benzyl-5-*t*-butoxycarbonyl-3-ethoxycarbonyl-4-oxo-2-pyrroline-5-propionate (0.7 g, 51.2%) as colorless plates (from diisopropyl ether), mp 102.0—103.0°. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1725, 1670. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 248 (13700), 317 (11600). MS *m/e*: 445 (M$^+$, 5.3%), 299 (100%). PMR ($\mathrm{CCl_4}$) δ: 1.18 (3H, t, J=7.2), 1.27 (3H, t, J=7.2), 1.41 (9H, s), 1.80—2.72 (4H, m, $\mathrm{CH_2CH_2COO}$), 4.03 (2H, q, J=7.2), 4.12 (2H, q, J=7.2), 4.50 (2H, s, $\mathrm{CH_2{-}Ph}$), 7.35 (5H, s), 8.29 (1H, s, $\mathrm{C_2}$–H). *Anal.* Calcd. for $\mathrm{C_{24}H_{31}NO_7}$: C, 64.70; H, 7.01; N, 3.14. Found: C, 64.68; H, 7.02; N, 3.21.

The fraction of lower *Rf* value gave diethyl 1-benzyl-3-ethoxycarbonyl-4-oxo-2-pyrroline-5,5-dipropionate (54 mg, 20.9%) as colorless leaflets [from benzene–cyclohexane (1: 1)], mp 157.0—158.0°. IR $\nu_{\mathrm{max}}^{\mathrm{KCl}}$ cm^{-1}: 1720, 1650. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (ε): 245 (15500), 313 (11500). MS *m/e*: 445 (M$^+$, 8.5%), 91 (100%). PMR (CDCl$_3$) δ: 1.23 (6H, t, J=7.0, OCH$_2$C$\underline{\mathrm{H}}_3\times2$), 1.31 (3H, t, J=7.0), 2.12 (8H, m, CH$_2$CH$_3$COO$\times$2), 4.09 (6H, q, J=7.0, OC$\underline{\mathrm{H}}_2$CH$_3\times3$), 4.46 (2H, s, CH$_2$–Ph), 7.38 (5H, s-like), 8.33 (1H, s, C$_2$–H). *Anal.* Calcd. for $C_{24}H_{31}NO_7$: C, 64.70; H, 7.01; N, 3.14. Found: C, 64.44; H, 7.00; N, 3.29.

The Michael Reaction of *t*-Butyl 3-Hydroxypyrrole-2-carboxylate (1b) with Ethyl Acrylate——A mixture of **1b** (100 ml), ethyl acrylate (0.15 ml), two drops of Triton B, and EtOH (10 ml) was refluxed for 5 hr. After the same work-up as in the case of **1e**, the residue was purified by PLC (benzene: EtOH=100: 15) to give ethyl 5-*t*-butoxycarbonyl-4-oxo-2-pyrroline-5-propionate (**12**) (50 mg, 32.3%) as colorless needles (from diisopropyl ether–acetone), mp 136.5—137.5°, and diethyl 5-*t*-butoxycarbonyl-4-oxo-2-pyrroline-1,5-dipropionate (**13**) (110 mg, 52.5%) as a colorless oil. Compound **12**: IR $\nu_{\mathrm{max}}^{\mathrm{KCl}}$ cm^{-1}: 3170, 1725, 1650. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (ε): 318 (7000). MS *m/e*: 283 (M$^+$, 1.8%), 57 (100%). PMR (CDCl$_3$) δ: 1.37 (3H, t, J=7.2), 1.47 (9H, s), 1.8—2.8 (4H, m, CH$_2$CH$_2$COO), 4.14 (2H, q, J=7.2), 5.18 (1H, d, J=3.6, C$_3$–H), 6.10 (1H, br, NH), 8.12 (1H, t, J=3.6, C$_2$–H). *Anal.* Calcd. for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.49; N, 4.94. Found: C, 59.23; H, 7.46; N, 5.03. Compound **13**: IR $\nu_{\mathrm{mxa}}^{\mathrm{CCl_4}}$ cm^{-1}: 1744, 1690. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (ε): 330 (9800). MS *m/e*: 383 (M$^+$, 2.6%), 57 (100%). PMR (CCl$_4$) δ: 1.24 (3H, t, J=6.8), 1.27 (3H, t, J=6.8), 1.43 (9H, s), 1.7—2.5 (4H, m, C–CH$_2$CH$_2$COO), 2.57 (2H, t, J=6.6, NCH$_2$C$\underline{\mathrm{H}}_2$COO), 3.53 (2H, t, J=6.6, NC$\underline{\mathrm{H}}_2$CH$_2$COO), 4.06 (2H, q, J=6.8), 4.14 (2H, q, J=6.8), 4.94 (1H, d, J=3.6, C$_3$–H), 7.97 (1H, d, J=3.6, C$_2$–H). *Anal.* Calcd. for $C_{19}H_{29}NO_7$: C, 59.51; H, 7.62; N, 3.65. Found: C, 59.00; H, 7.63; N, 3.89.

Ethyl 4-Bromo-1-methyl-3-hydroxypyrrole-2-carboxylate (15)——To a solution of **1c** (690 mg) in abs. CHCl$_3$ (20 ml) was added dropwise with ice-cooling a solution of bromine (650 mg) in abs. CHCl$_3$ (50 ml) during 2.5 hr. The reaction mixture was washed with a mixture of 10% Na$_2$S$_2$O$_3$ and satd. NaHCO$_3$ solution, and dried. After removal of the solvent, the residue was recrystallized from EtOH to give **15** (0.7 g, 69.1%) as colorless plates, mp 89.5—90.5°. IR $\nu_{\mathrm{max}}^{\mathrm{KCl}}$ cm^{-1}: 3258, 3115, 1644. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (ε): 265 (16700). PMR (CCl$_4$) δ: 1.41 (3H, t, J=7.2), 3.74 (3H, s), 4.35 (2H, q, J=7.2), 6.49 (1H, s, C$_5$–H), 7.93 (1H, s, OH). *Anal.* Calcd. for $C_8H_{10}BrNO_3$: C, 38.73; H, 4.06; N, 5.65. Found: C, 38.29; H, 4.04; N, 5.68.

Ethyl 4,5-Dibromo-1-methyl-3-hydroxypyrrole-2-carboxylate (16)——To a solution of **1c** (0.5 g) in abs. CHCl$_3$ (15 ml) was added dropwise a solution of bromine in abs. CHCl$_3$ until the color of bromine was persistent. After the same work-up as in the case of **15**, the residue was recrystallized from EtOH to give **16** (0.6 g, 62.0%) as colorless needles, mp 64.0—65.0°. IR $\nu_{\mathrm{max}}^{\mathrm{KCl}}$ cm^{-1}: 3305, 1658. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (ε): 275 (15800). PMR (CCl$_4$) δ: 1.42 (3H, t, J=7.2), 3.81 (3H, s), 4.37 (2H, q, J=7.2), 8.22 (1H, s, OH). *Anal.* Calcd. for $C_8H_9Br_2NO_3$: C, 29.38; H, 2.77; N, 4.28. Found: C, 29.35; H, 2.78; N, 4.50.

Diethyl 5-Bromo-1-methyl-3-hydroxypyrrole-2,4-dicarboxylate (18)——Compound **18** was prepared in a manner similar to that for **16** starting from 3.0 g of diethyl 1-methyl-3-hydroxypyrrole-2,4-dicarboxylate[1] (**17**). Recrystallization of the crude product from EtOH gave **18** (3.0 g, 75.3%) as colorless plates, mp 71.0—72.0°. IR $\nu_{\mathrm{max}}^{\mathrm{KCl}}$ cm^{-1}: 3145, 1695, 1678. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (ε): 233 (23000), 267 (14000). PMR (CCl$_4$) δ: 1.38 (3H, t, J=7.2), 1.40 (3H, t, J=7.2), 3.90 (3H, s), 4.28 (2H, q, J=7.2), 4.34 (2H, q, J=7.2), 9.02 (1H, s, OH). *Anal.* Calcd. for $C_{11}H_{14}BrNO_5$: C, 41.27; H, 4.41; N, 4.38. Found: C, 41.27; H, 4.46; N, 4.56.

Ethyl 5-Bromo-1-methyl-3-hydroxypyrrole-2-carboxylate (19)——To a solution of **18** (0.6 g) in EtOH (10 ml) was added a solution of NaOH (0.38 g) in EtOH (20 ml), and the mixture was refluxed under N$_2$ for 1 hr. After the addition of water (5 ml), the reaction mixture was refluxed for additional 3 hr, and followed by addition of water (10 ml) and acidified with conc. HCl to Congo red. The resulting precipitate was collected, washed, and dried *in vacuo* (0.47 g). The crude acid (0.47 g) was heated in hexamethylphosphoric triamide (20 ml) at 150—200° for 5 min. The reaction mixture was poured into water, and extracted with benzene. The extract was washed with 1% H$_2$SO$_4$, satd. NaHCO$_3$, dried and evaporated. The residue was purified by PLC (benzene: EtOH=10: 1) to give **19** (0.14 g, 18.1% from **18**) as colorless needles (from EtOH), mp 43.0—44.0°. IR $\nu_{\mathrm{max}}^{\mathrm{KCl}}$ cm^{-1}: 3250, 1645. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (ε): 272 (18600). PMR (CCl$_4$) δ: 1.42 (3H, t, J=7.2), 3.76 (3H, s), 4.36 (2H, q, J=7.2), 5.80 (1H, s, C$_4$–H), 8.08 (1H, s, OH). High resolution mass spectrum[26] *m/e*: 246.9836, 248.9822 (M$^+$, M$^+$+2, Calcd. for $C_8H_{10}BrNO_3$: 246.9844, 248.9824). Compound **19** was easily converted to the dibromide (**16**) by bromination in a usual manner.

Ethyl 4-Dimethylaminomethyl-1-methyl-3-hydroxypyrrole-2-carboxylate (20)——To a stirred solution of **1c** (0.2 g) in EtOH (20 ml) was added 37% formalin (0.19 g) and 40% dimethylamine solution (0.27 g), and the mixture was stirred for additional 1 hr. The solvent was removed to dryness under reduced pressure to give **20** (0.27 g) as an oil. PMR (CDCl$_3$) δ: 1.40 (3H, t, J=7.0), 2.24 (6H, s, NMe$_2$), 3.31 (2H, s, NCH$_2$–), 3.74 (3H, s), 4.37 (2H, q, J=7.0), 6.51 (1H, s, C$_5$–H). Picrate: yellow needles (from EtOH), mp 173.5—174.5° (dec.). *Anal.* Calcd. for $C_{17}H_{21}N_5O_{10}$: C, 44.84; H, 4.65; N, 15.38. Found: C, 44.81; H, 4.73; N, 15.19.

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[26] High resolution mass spectrum was taken with JEOL JMS–01SG mass spectrometer. The authors are grateful to Professor M. Itoh and Miss K. Saiki of Kobe Women's College of Pharmacy for their help and suggestions in the high resolution mass spectrum measurement.

Ethyl 4-Dimethylaminomethyl-1-methyl-3-hydroxypyrrole-2-carboxylate Methiodide (**21**)——To a solution of **20** (1.53 g) in dry ether (5 ml) was added dropwise a solution of methyl iodide (8.39 g) in dry ether (5 ml). Compound **21** was obtained in quantitative yield after evaporation of ether and excess methyl iodide. The product was recrystallized from acetonitrile–ether to give pale yellow crystals, mp 158.0—160.0°. IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 3300, 2900, 1700. PMR ($CDCl_3$) δ: 1.43 (3H, t, J=6.8), 3.34 (9H, s, Me_3N^+–), 3.82 (3H, s), 4.40 (2H, q, J=6.8), 4.65 (2H, s, –CH_2N^+), 7.38 (1H, s, C_5–H). *Anal.* Calcd. for $C_{12}H_{21}IN_2O_3$: C, 39.14; H, 5.75; N, 7.61. Found: C, 39.21; H, 5.75; N, 7.56.

Cyanation of the Methiodide (**21**)——To a stirred solution of **21** (0.6 g) in dimethoxyethane (15 ml) was added powdered sodium cyanide (0.4 g). After the addition of water (5 ml), the stirring was continued for 24 hr. To the reaction mixture was added water (20 ml), and the mixture was extracted with $CHCl_3$. After removal of the solvent from the extract, the residue was purified by PLC (benzene: EtOH=10: 1) to give ethyl 4-cyanomethyl-1-methyl-3-hydroxypyrrole-2-carboxylate (**22**) (43 mg, 12.7%), and ethyl 1-methyl-4-(3-cyanomethyl-5-ethoxycarbonyl-1-methyl-4-oxo-2-pyrrolin-5-yl)methyl-3-hydroxypyrrole-2-carboxylate (**23**) (85 mg, 26.8%), and a trace amount of ethyl 4-[3-(3-cyanomethyl-5-ethoxycarbonyl-1-methyl-4-oxo-2-pyrrolin-5-yl)methyl-5-ethoxycarbonyl-1-methyl-4-oxo-2-pyrrolin-5-yl]methyl-1-methyl-3-hydroxypyrrole-2-carboxylate (**24**). Compound **22**: colorless plates (from diisopropyl ether), mp 122.0—123.5°. IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 3350, 2225, 1673. MS *m/e*: 208 (M^+, 48.5%), 162 (100%). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 265 (19900), PMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.0), 3.49 (2H, s, CH_2CN), 3.76 (3H, s), 4.38 (2H, q, J=7.0), 6.62 (1H, s, C_5–H), 8.05 (1H, br–s, OH). *Anal.* Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C 57.48; H, 5.76; N, 13.72. Compound **23**: pale yellow glass. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3480, 2240, 1730, 1702, 1665, 1643. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 267 (18600), 338 (7400). MS *m/e*: 389 (M^+, 6.8%), 139 (100%). PMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.0), 1.36 (3H, t, J=7.0), 3.10, 3.14 (2H, each s), 3.21 (3H, s), 3.25, 3.29 (2H, each s), 3.63 (3H, s), 4.25 (2H, q, J=7.0), 4.32 (2H, q, J=7.0), 6.30 (1H, s), 7.72 (1H, s), 8.18 (1H, br). Compound **24**: pale yellow glass. IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 3480, 2248, 1732, 1660. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 266 (18500), 332 (14700). MS *m/e*: 570 (M^+, <1%), 182 (100%). PMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0), 1.32 (3H, t, J=7.0), 1.38 (3H, t, J=7.0), 2.94 (2H, s), 2.80—3.65 (6H, m), 2.99 (3H, s), 3.09 (3H, s), 3.75 (3H, s), 4.19 (4H, q, J=7.0), 4.38 (2H, q, J=7.0), 6.43 (1H, s), 7.19 (1H, s), 7.60 (1H, s), 7.80 (1H, br).

The Mannich Reaction of 15——A mixture of **15** (0.80 g), EtOH (20 ml), 37% formalin (0.52 g) and 40% dimethylamine solution (0.73 g) was stirred for 14 hr at room temperature. After removal of the solvent to dryness under reduced pressure, the oily residue was dissolved in acetonitrile (15 ml), followed by the addition of a solution of NaCN (1.58 g) in H_2O (15 ml). To the resulting mixture was added a solution of MeI (2 ml) in acetonitrile (20 ml) during 1 hr with stirring. After 10 hr, the acetonitrile was evaporated, and the residue was extracted with $CHCl_3$. After removal of the solvent from the $CHCl_3$ layer, the resulting residue was purified by PLC ($CHCl_3$: EtOH=50: 1) to give the raw monocyanide as crystals (71 mg) and ethyl 4-cyano-5-cyanomethyl-1-methyl-3-hydroxypyrrole-2-carboxylate (**26**) (116 mg, 15.4%) as colorless needles (from EtOH), mp 137.0—138.0°. The raw crystals of the monocyanide was purified by PLC (first in cyclohexane: EtOH=10: 1 and next in benzene) to give ethyl 4-bromo-5-cyanomethyl-1-methyl-3-hydroxypyrrole-2-carboxylate (**25**) (25 mg, 3.0%) as colorless needles (from cyclohexane), mp 89.0—90.0°. The aqueous layer was acidified with 10% H_2SO_4, and extracted with $CHCl_3$. The extract was evaporated, and the crystalline residue was recrystallized from EtOH to give **26** (110 mg). The total yield of **26** was 30.1%. Compound **26**: IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 3345, 2220, 1673. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 213 (9800), 267 (16300), 294 (9500). MS *m/e*: 233 (M^+, 15.6%), 187 (100%). PMR ($CDCl_3$) δ: 1.46 (3H, t, J=7.0), 3.62 (2H, s, CH_2CN), 3.93 (3H, s), 4.47 (2H, q, J=7.0), 8.05 (1H, br–s, OH). *Anal.* Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.46; H, 4.83; N, 18.33. Compound **25**: IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 3380, 2225, 1712. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 269 (14600). PMR ($CDCl_3$) δ: 1.39 (3H, t, J=7.0), 3.86 (3H, s), 3.98 (2H, s), 4.37 (2H, q, J=7.0), 8.07 (1H, br). High resolution mass spectrum[27] *m/e*: 285.9962, 287.9938 (M^+, M^++2, Calcd. for $C_{10}H_{11}BrN_2O_3$: 285.9953, 287.9933).

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27) High resolution mass spectrum was taken with Hitachi Hi- Res. Mass System. The authors are grateful to Dr. Y. Nakagawa of Shionogi Research Laboratory, Shionogi and Co., Ltd. for his help and suggestions in the high resolution mass spectrum measurement.