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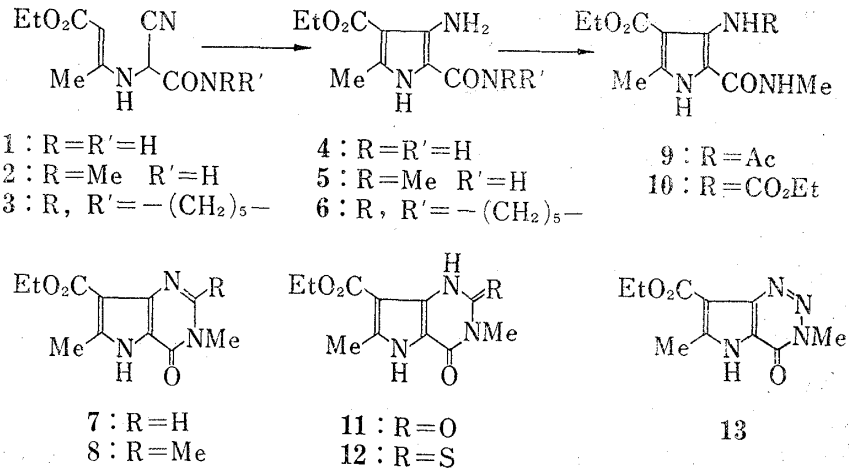
Intramolecular Reactions of Enaminonitriles. II.[1] Synthesis of New 3-Aminopyrrole-2-carboxamides—A New Route to Pyrrolo[3,2-*d*]pyrimidines

As an extension of our studies on the intramolecular reactions of certain enaminonitriles,[1] we have investigated with enaminonitriles (**1**—**3**) carrying a carboxamide group in the molecules. Attempts were made to obtain new 3-aminopyrrole-2-carboxamides (**4**—**6**) by the use of intramolecular addition of enamine to nitrile group,[2] a novel method for preparation of the compounds, and to further convert such an appropriate product as **5** into several new pyrrolo[3,2-*d*]pyrimidines. The conversion is also of interest because there has been no report of pyrrolo[3,2-*d*]pyrimidine synthesis starting from 3-aminopyrroles;[3] this is undoubtedly due to the absence of good preparative method for suitable 3-aminopyrroles. We now preliminarily report successful syntheses of new aminopyrrolecarboxamides (**4**—**6**) and pyrrolo[3,2-*d*]pyrimidines (**7**, **8**, **11** and **12**). In addition to this, a new pyrrolo[3,2-*d*]-*v*-triazine derivative (**13**) has been synthesized.



1 : R=R'=H
2 : R=Me R'=H
3 : R, R'=$-(CH_2)_5-$

4 : R=R'=H
5 : R=Me R'=H
6 : R, R'=$-(CH_2)_5-$

9 : R=Ac
10 : R=CO_2Et

7 : R=H
8 : R=Me

11 : R=O
12 : R=S

13

Thus, enamines (**1**—**3**), prepared by condensation of ethyl acetoacetate with the aminocyanoacetamides,[1,4] were treated with NaOEt in ethanol to cyclize to the expected products (**4**—**6**), respectively: **4**, $C_9H_{13}O_3N_3$, mp 229—230°; **5**, $C_{10}H_{15}O_3N_3$, mp 213—215°; **6**, $C_{14}H_{21}O_3N_3$, mp 158—159°. Though the yield of **4** was rather poor (30%), the latter two compounds were obtained in about 75% yields. There was no need of the substitution at the methine group of enamines (**1**—**3**) with electrophiles such as acrylic acid derivatives or methyl vinyl ketone.[1] The structures of the new aminopyrrolecarboxamides (**4**—**6**) have been established

1) Part I: T. Murata, T. Sugawara, and K. Ukawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 2571 (1973).
2) As for the direction of intramolecular reaction of **1**—**3**, it was reasonably anticipated that the addition of enamine to the nitrile group is favourable because the amidocarbonyl in the enamines should be stabilized against nucleophiles by a delocalization (O=C–NRR' ⟷ O^-–C=N^+RR').
3) 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 *a*) K. Tanaka, T. Sugawa, R. Nakamori, Y. Sanno, Y. Ando, and K. Imai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1024 (1964); *b*) H. Fenner and H. Motschall, *Tetrahedron Letters*, **1971**, 4185.
4) The aminocyanoacetamides were prepared by reduction of the corresponding oximinocyanoacetamides, respectively. *cf.* L.H. Smith, Jr. and P. Yates, *J. Am. Chem. Soc.*, **76**, 6080 (1954); C.S. Miller, S. Gurin, and D.W. Wilson, *ibid.*, **74**, 2892 (1952); O. Touster, "Organic Reactions," Vol. 7, R. Adams ed., John Wiley & Sons, Inc., New York, 1953, p. 327.

on the basis of physico-chemical data; particularly, nuclear magnetic resonance (NMR) spectra of the compounds provided an unequivocal proof showing the 3-amino and pyrrolic NH protons near 5 and 11 ppm,[1] respectively (δ, DMSO-d_6, 100 Mc).

As might have been expected, **5** was easily transformed into new pyrrolo[3,2-*d*]pyrimidines by following reactions: heating of **5** with formic acid gave a 4-oxo-3,4-dihydropyrrolo[3,2-*d*]-pyrimidine derivative (**7**), $C_{11}H_{13}O_3N_3$, mp 288°, UV λ_{max}^{EtOH} mμ (log ε): 234.5 (4.70) and 256 (shoulder, 3.92), in 90% yield. Support for the structure of product (**7**) comes from its NMR spectrum which shows the C_2-proton at 9.27 ppm as a sharp singlet (CF_3CO_2D). The corresponding 2-methyl derivative (**8**), $C_{12}H_{15}O_3N_3$, mp 270°, was obtained by acetylation of **5** (Ac_2O–NaOAc) followed by NaOEt-induced cyclization of the resulting acetate (**9**), $C_{12}H_{17}O_4N_3$, mp 243—245°. **8** could also be obtained by the reaction of **5** with 2,4-pentanedione in ethanolic hydrochloric acid. Ethyl chloroformate-pyridine reacted with **5** to yield urethane (**10**), $C_{13}H_{19}O_5N_3$; the latter upon treatment with NaOEt cyclized quantitatively to **11**,[5] $C_{11}H_{13}O_4N_3$, mp 305°, UV λ_{max}^{EtOH} mμ (log ε): 229.5 (4.48) and 270 (4.00); $\lambda_{max}^{0.1N\cdot HCl}$ mμ: 231 and 274; $\lambda_{max}^{0.1N\cdot NaOH}$ mμ: 242 and 285. A 2-thione compound (**12**), $C_{11}H_{13}O_3N_3S$, mp 257°, was readily prepared by the reaction of **5** with potassium xanthogenate in pyridine and subsequent treatment with aqueous hydrochloric acid; the thioamide structure of **12** was based on the presence of IR bands at 3360, 1580 and 1310 cm^{-1}.[6] Further, **5**, when treated with sodium nitrite in aqueous hydrochloric acid, afforded a pyrrolotriazine derivative **13**, $C_{10}H_{12}O_3N_4$, mp 242—244°, IR ν_{max}^{Nujol} cm^{-1}: 1690 and 1665 (carbonyls), UV λ_{max}^{EtOH} mμ (log ε): 234 (4.53) and 277 (3.68).

Details and discussion of these reactions will be dealt later.

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5) Though there lies obscurity in the assignment of infrared (IR) carbonyl bands of the compound, we allotted the 2,4-dioxo structure to the compound by its analogy with several 2,4-dioxo-pyrrolo-[3,2-*d*]pyrimidines[3a] as well as with certain heterocycles related to pyrimidine-2,4-diones. *cf.* A. Katritzky and J.M. Lagowsky, "Advances in Heterocyclic Chemistry," Vol. 1, A. Katritzky ed., Academic Press Inc., New York, 1963, p. 339.

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