reaction of *d-l*-V with ammonia-saturated methanol at 40° in a sealed tube for 2.2 hr. followed by careful chromatography on silica gel eluted with a mixture of *n*-hexane and acetone gave a colorless needles, mp 67°, $C_{24}H_{32}O_4$, $[\alpha]_D^{15}$ +20.0° (c=0.25, $CHCl_3$). This was confirmed to be identical with *d*-benzylgingerol (*d*-II), mp 67°, $[\alpha]_D^{16}$ +21.6° (c=1.0, $CHCl_3$), derived from natural gingerol by comparison of IR spectra (Nujol) and mixed melting point determination.

Reductive debenzylation of *d*-II gave a phenolic oil,[1] $[\alpha]_D^{27}$ +23.9° (c=1.0, $CHCl_3$), whose IR and NMR spectra were superimposable on those of natural gingerol. For the sake of further confirmation of the synthetic oil, the oil was treated with 2,4-dinitrofluorobenzene to give a slightly yellow needles, mp 84°, $C_{23}H_{28}O_8N_2$, $[\alpha]_D^{14}$ +13.8° (c=0.25, $CHCl_3$). This was identical with DNP-gingerol (VI), mp 84°, $[\alpha]_D^{16}$ +14.0 (c=1.0, $CHCl_3$), derived from natural gingerol in all respects.

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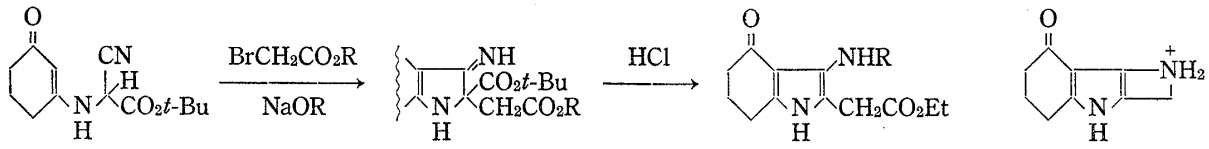
Intramolecular Reactions of Enaminonitriles. I. A Novel Synthesis of New β-Aminopyrroles and Related Heterocycles[1]

Chemistry of β-aminopyrroles has little been studied apparently owing to the scanty of versatile synthetic procedure for the compounds. Thus only a few β-aminopyrroles have been prepared by nitration or nitrosation of appropriate α-substituted pyrroles followed by reduction, a classical method.[2] We now wish to describe simple routes for several new β-aminopyrroles and related compounds including substituted 3-amino-4-oxo-4,5,6,7-tetrahydroindoles (**5**, **15**, **18**), pyrido[3,2-*b*]indole (**9**) and pyrrolo[3,2-*b*] pyridine derivatives (**25**, **26**),[3] which have a distinctive feature comprising an intramolecular addition of an enamine to a nitrile group.[4]



1 — 2: R=Me, 3: R=Et — 5: R=H, 6: R=Ac — 4

Chart 1

1) Satisfactory analyses were obtained for all new compounds. Melting points were measured on Kofler block and uncorrected.
2) K. Schofield, "Hetero-Aromatic Nitrogen Compounds-Pyrroles and Pyridines, "Butterworths & Co., London, 1967, p. 27; F. Troxler, "Chemistry of Heterocyclic Compounds," (A. Weissberger and E.C. Taylor ed.), Vol. 25, Part II, W. Houlian ed., John Wiley & Sons, Inc., New York, 1972, p. 210.
3) R.E. Willete, "Advances in Heterocyclic Chemistry," Vol. 9, A.R. Katritzky and A.J. Boulton ed., Academic Press, New York, 1968, p. 27.
4) A.I. Meyers and J.C. Sircar, "The Chemistry of the Cyano Group," Z. Rappoport ed., Interscience Publishers, London, 1970, p. 341.

Initial studies were carried out using enamine **1**, readily prepared from cyclohexane-1,3-dione and *tert*-butyl aminocyanoacetate.[5] Our idea was the substitution at the methine of **1** with electrophiles. First, **1** was treated with methyl or ethyl bromoacetate and two equivalents of the corresponding sodium alcohoxide to obtain compounds **2**, mp 157—158° and **3**, mp 131—132°, respectively, in about 40% yield (Chart 1). Structures (**2**, **3**), alloted to them, receive support from physico-chemical measurements: Both **2** and **3** have a base peak at *m/e* 163 ($C_9H_{11}N_2O^+$, a fragment shown by **4**) as well as a strong peak at *m/e* 57 (*tert*-Bu^+) in the mass spectra. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$, 100 Mc) of **3** shows two one-proton singlets ascribable to two NH protons at 7.54 and 8.07 ppm (δ), respectively; no olefinic proton signal was observed. The NMR spectrum of **2** exhibits an AB system, centered at 2.40 and 3.50 ppm, respectively (J=19 Hz), due to the methylene group at C_2.

Treatment of **3** with hydrogen chloride generated an unstable 3-amino-4-oxotetrahydroindole-2-acetic acid ester **5**; the latter was acetylated to **6**, mp 165°. The NMR spectrum of **6** now shows the methylene protons at C_2 at 3.54 ppm as a singlet. Above reactions **1**→**2** (**3**) should reasonably involve the substitution of the methine in **1** by the bromoacetate followed by an intramolecular addition of the enamine to the nitrile, since **1** did not cyclize with only sodium alcohoxide.

A modification of this process provides a route to a new pyrido[3,2-*b*]indole derivative **9** according to the sequence shown in Chart 2. Treatment of **1** with ethyl acrylate and NaOEt in warm alcohol gave a product mp 310° (35% yield) to which we assigned the structure **9**. In the NMR spectrum (DMSO-d_6) **9** shows two singlets assignable to two NH protons at 8.06 and 11.06 ppm, respectively. Alkylation of **9** with dimethyl sulfate-NaOEt gave a N-methyl derivative **10**, mp 223°. Benzylation (benzyl chloride-K_2CO_3) of **9** yielded **11**, mp 182—183°; the latter was methylated (dimethyl sulfate-NaOEt) to **12**, mp 166—167°. Debenzylation of **12** with sodium in liquid ammonia led to another N-methyl derivative **13**, mp 220—222°.[6] Since alkylation with a base must take place preferentially at the pyrrole

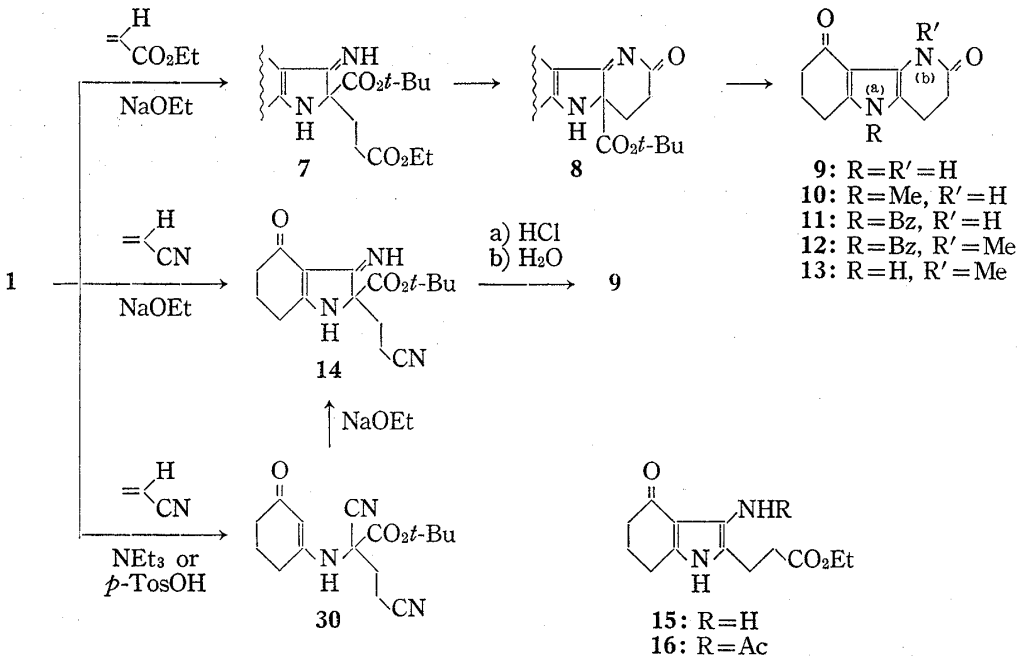


Chart 2

5) The compound was prepared in the manner described for ethyl α-aminocyanoacetate. *cf.* J.W. Cornforth, "The Chemistry of Penicillin," H.T. Clarke, J.R. Johnson and R. Robinson ed., Princeton Univ. Press, Princeton, New Jersey, 1949, p. 725.

6) Differentiation between **10** and **13** can be done by comparison of infrared (IR) and NMR spectra.

nitrogen $N_{(a)}$, which carries a proton more acidic than an amide proton, it is reasonable to conclude that compound **10** should be the $N_{(a)}$-methyl derivative, while **13** a $N_{(b)}$-methyl compound. The reactions support the structure of **9**. Amide structures for the compounds (**9**—**13**) were based on spectral evidence.[7] Confirmation of the structure **9** comes from cyclization of compound **14** which was prepared by condensation of **1** with acrylonitrile; **14** upon treatment with gaseous hydrogen chloride yielded **9**. In addition to this, alcoholysis of **9** with ethanolic hydrochloric acid afforded **15**; acetate **16**, mp 165°.

Reaction of **1** with methyl vinyl ketone (MVK) in the presence of NaOEt provides a good method for new 3-amino-4-oxo-4,5,6,7-tetrahydroindole-2-carboxylic acid *tert*-butyl ester **18**, mp 218—220°, (40% yield, Chart 3). The NMR spectrum (DMSO-d_6) of **18** clearly shows a two-proton singlet due to the amino group at 5.50 ppm; the pyrrole NH proton appears at 11.00 ppm. Deamination of **18** was carried out by diazotation followed by heating of the resulting diazoindolenine **19**,[8] mp 109—110°, with ethanolic sulfuric acid. The product **20**, mp 182—184°, exhibits the C_3-proton at 6.81 ppm as a doublet (J=2 Hz), thus providing an unequiovocal proof for the structure of **18**. **1** did not cyclize to **18** with only a base. Thus it can be concluded that the anion formation at the methine of **1** is unfavourable to the cyclization. **18** must arise from an intermediate **17**, which corresponds to **7** and **14**, by elimination of MVK moiety, a sequence reminiscent of reverse Michael reaction.[9] In accord with the assumption the reactions **1**→**9** and **1**→**14** were found to be accompanied by the formation of **18**; treatment of **14** with NaOEt in warm ethanol gave **18**.

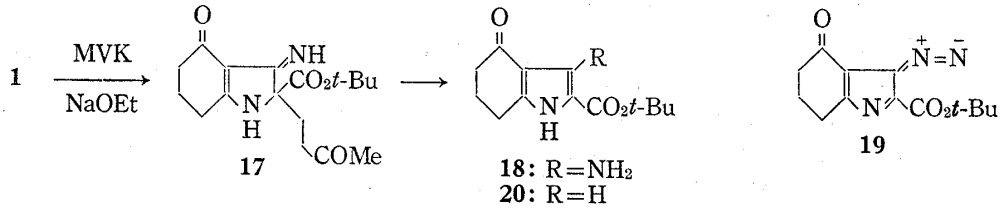


Chart 3

Above novel syntheses were then applied to the enamines (**21** and **22**),[10] obtained by condensation of the acetoacetates with *tert*-butyl α-aminocyanoacetate (Chart 4). Compounds **21** and **22** were treated with ethyl acrylate in cold ethanol (NaOEt) to give **23** and **24**, respectively (40%). The products were then transformed into **25**,[11] mp 164—166° and **26**, mp 189—190°, respectively by thermolysis. The conversions (**23**→**25** and **24**→**26**) were also readily accomplished by acids such as formic acid or trifluoroacetic acid. New 3-aminopyrrole derivatives (**27** and **28**) have been prepared by the reactions of **21** and **22**, respectively with MVK in the same manner as the sequence **1**→**18** (**27**, mp 193°, 70% yield, **28**, mp 181—182°,

7) **10** clearly shows two carbonyl bands at 1640 and 1675 cm^{-1}, respectively in the IR spectrum (KBr); the former is reasonably assignable to the conjugated carbonyl, while the latter to the amide carbonyl. Similarly, **13** exhibits bands at 1630 and 1650 cm^{-1}. In the spectra of **9** and **12**, almost overlapped bands appear near 1650 cm^{-1}. Further, ultraviolet (UV) spectra of **9**—**13** are almost identical with each other showing two maxima at 250 (ε, *ca.* 16000) and 310 mμ (ε, *ca.* 3100), respectively.

8) The compound is characterized by a strong IR band at 2150 cm^{-1} (Nujol). *cf.* 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.

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

10) In Chart 4, **21** and **22** 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.

11) The IR spectrum (Nujol) of **25** showed bands at 1690 (ester C=O) and 1645 cm^{-1} (amide C=O); the latter shifted to 1620 cm^{-1} in the dehydrogenation product, mp 205—207°, which was obtained by the reaction of **25** with chloranil or DDQ.

50%). **27** has been correlated to authentic 4-ethoxycarbonyl-5-methylpyrrole-2-carboxylic acid **29**,[12] mp 238—240°, through deamination and subsequent removal of the *tert*-butyl group by formic acid.

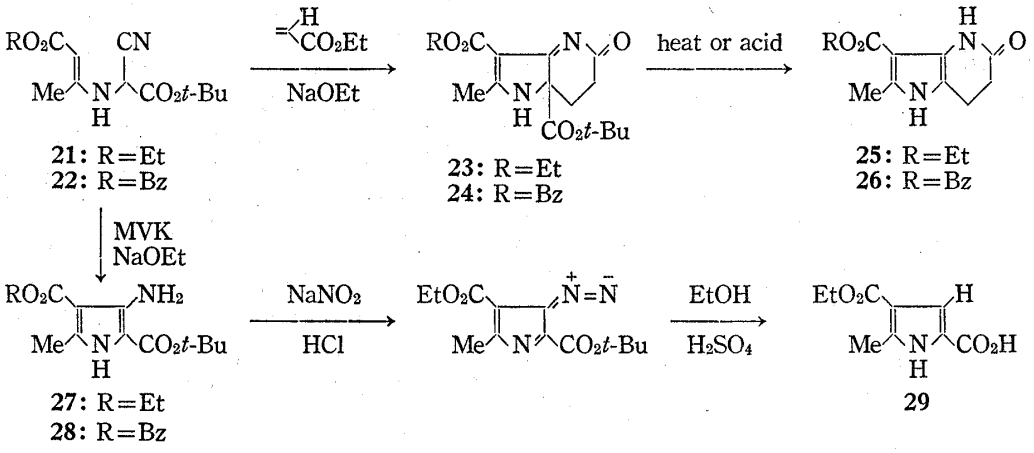


Chart 4

Enamine **1** was alkylated with acrylonitrile in the presence of triethylamine or *p*-toluenesulfonic acid to give **30**, mp 151—153°; the latter upon treatment with NaOEt in ethanol cyclized to **14** (Chart 2). This clearly demonstrates the sequence of the 3-iminopyrroline syntheses above described. Attension was then turned to the scope and limitation of the intramolecular addition of enamine to nitrile group (Chart 5). Enamines (**31**—**35**), prepared analogously to **21**, were treated with ethyl acrylate and two equivalents of NaOEt in cold ethanol. The ethylester **31** gave a product, mp 163—165°, to which we assigned the structure **37** in 70% yield. Neither a compound corresponding to **23**, menitoned above, nor **25** was obtained. The undecanylester **35** also afforded **37** as a sole product, whereas enamines (**32**—**34**) which possess at least one secondary methyl at the carbon attached to the alkoxyl oxygen yielded a mixture of **37** and **25**. **21** did not give **37**. Since compounds (**31**—**35**) show no tendency to cyclize with only NaOEt as in the case of **21**, formation of **37** above described must involve the substitution at the methine by the acrylate followed by intramolecular attack of the enamine on the ester carbonyl β to the cyano group. Thus two intramolecular reactions in an intermediate **36** have been demonstrated; one which against the nitrile and the other on the ester carbonyl. A bulky *tert*-butyl group must prevent the latter reaction so as to favour the addition of enamine to nitrile. A neighbouring group effect is manifest in the case. The structure of **37** has been established on the basis of following data: **37** has UV maxima at 236 (ε, 13500) and 299 mμ (8500), respectively, showing a close similarity with known 3-ethoxycarbonyl-2-methyl-2-pyrrolin-4-one.[13] Evidence supporting the structure was obtained by a revearse Michael reaction of **37**, which gives a new 2-cyano-3-hydroxypyrrole derivative **40**: **37** upon treatment with sodium methylsulfinylmethide ($NaCH_2SOCH_3$) in DMSO,[14] at room temperature yielded **40** in 64% yield. Compound **40**, mp 179—181°, UV λ_{max}^{EtOH} mμ (ε): 224 (31400); 242 (shoulder, 14900), IR ν_{max}^{Nujol} cm^{-1}: 3230 (NH and OH); 2220 (CN), gives compound **37** upon reaction with ethyl acrylate and NaOEt.

Reactions of enamine **31** with acrylonitrile or MVK in the presence of NaOEt yielded **38**,[15] mp 202—204° and **39**, mp 172—177°, respectively. The structures of the products

12) The compound was obtained by carboxylation of 3-ethoxycarbonyl-2-methylpyrrole. *Cf.* H. Fischer and M. Hussong, *Ann.*, **492**, 128 (1932).
13) E. Benary and B. Silbermann, *Ber.*, **46**, 1363 (1913); J. Davoll, *J. Chem. Soc.*, **1953**, 3802.
14) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, 1967, p. 310
15) Compound **38** also afforded **40** upon treatment with $NaCH_2SOCH_3$ at room temperature. **40** can be obtained from **31** in 65% yield without isolation of the intermediate **38**.

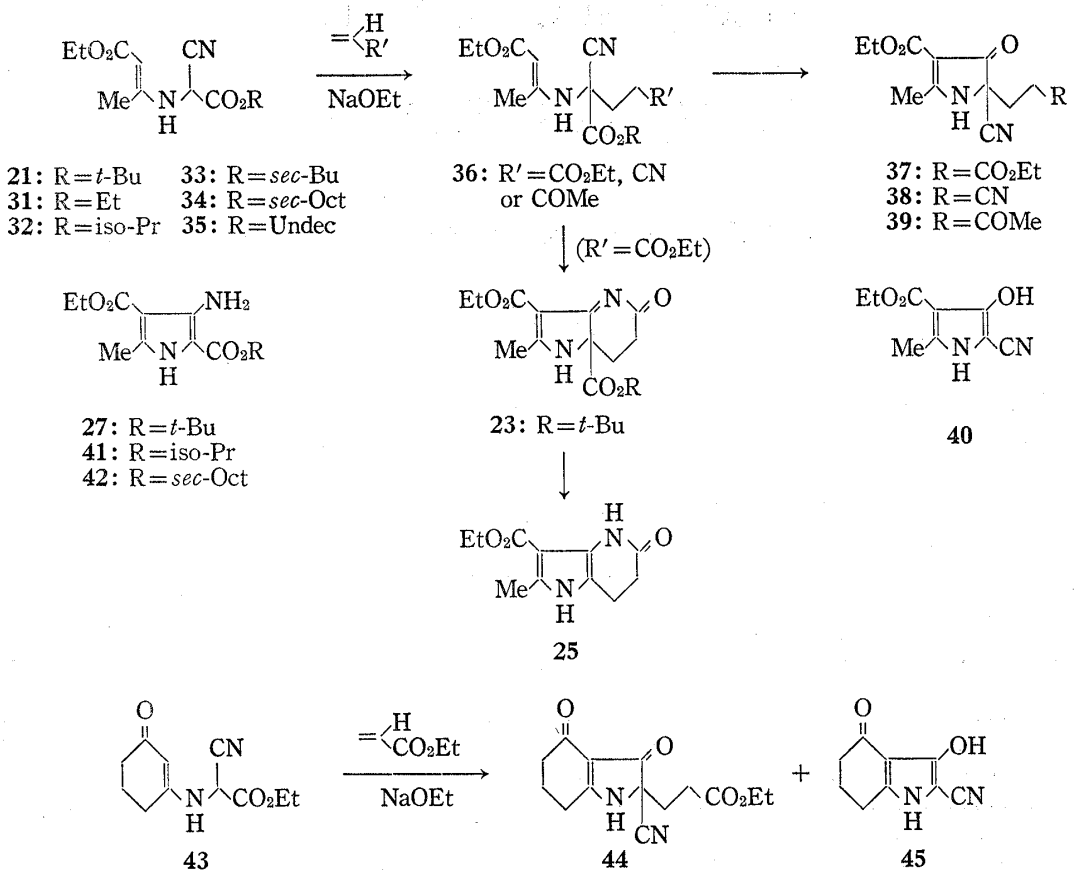


Chart 5

(**38** and **39**) were based on their UV spectra, respectively, which are identical with that of **37**. Reactions of **32** or **34** with MVK yielded a mixture of **39** and the corresponding 3-amino-4-ethoxycarbonyl-5-methylpyrrole-2-carboxylic acid esters, respectively; iso-propylester **41**, mp 161—162°; *sec*-octylester **42**, mp 91—92°. Again this shows the two intramolecular reactions had occurred. As shown in Chart 5, enamine **43**, when treated with ethyl acrylate and NaOEt gave new 2-cyano-3-hydroxy-4-oxo-4,5,6,7-tetrahydroindole **45**, mp 298°, UV λ_{max}^{EtOH} mμ (ε): 235.5 (30400); 250 (shoulder, 17700), IR ν_{max}^{KBr} cm^{-1}: 2200 (CN); 1642 (C=O), besides 3,4-dioxohexahydroindole derivative **44**, mp 217—221°, UV λ_{max}^{EtOH} mμ (ε): 255 (15300); 291 (8700). The combined yield of **44** and **45** was about 40%.

Details of these reactions will be reported elsewhere.

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