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°, $C_{24}H_{32}O_4$, $[\alpha]_D^{25} +20.0^\circ$ ($c=0.25$, $CHCl_3$). This was confirmed to be identical with *d*-benzylgingerol (*d*-II), mp 67°, $[\alpha]_D^{25} +21.6^\circ$ ($c=1.0$, $CHCl_3$), 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⁾ $[\alpha]_D^{27} +23.9^\circ$ ($c=1.0$, $CHCl_3$), 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°, $C_{23}H_{28}O_8N_2$, $[\alpha]_D^{25} +13.8^\circ$ ($c=0.25$, $CHCl_3$). This was identical with DNP-gingerol (VI), mp 84°, $[\alpha]_D^{25} +14.0^\circ$ ($c=1.0$, $CHCl_3$), derived from natural gingerol in all respects.

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Received June 7, 1973

[Chem. Pharm. Bull.]
21(11)2571-2575(1973)

UDC 547.743.4.057 : 547.339.2.04

Intramolecular Reactions of Enaminonitriles. I. A Novel Synthesis of New β -Aminopyrroles and Related Heterocycles¹⁾

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⁾

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. Houlihan ed., John Wiley & Sons, Inc., New York, 1972, p. 210.
- 3) R.E. Willeite, "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 aminocynoacetate.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 alkoxide to obtain compounds **2**, mp 157—158° and **3**, mp 131—132°, respectively, in about 40% yield (Chart 1). Structures (**2**, **3**), allotted 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 (CDCl₃, 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 C₂.

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 C₂ 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 alkoxide.

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-K₂CO₃) 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°. 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 -aminocynoacetate. 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 C₃-proton at 6.81 ppm as a doublet (*J*=2 Hz), thus providing an unequivocal 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 m μ (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. Attention 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**, mentioned 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 alkoxy 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 m μ (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 reverse Michael reaction of **37**, which gives a new 2-cyano-3-hydroxypyrrole derivative **40**: **37** upon treatment with sodium methylsulfinylmethide ($\text{NaCH}_2\text{SOCH}_3$) in DMSO,¹⁴⁾ at room temperature yielded **40** in 64% yield. Compound **40**, mp 179—181°, UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ): 224 (31400); 242 (shoulder, 14900), IR $\nu_{\text{max}}^{\text{Nujol}}$ 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 $\text{NaCH}_2\text{SOCH}_3$ 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 $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ): 235.5 (30400); 250 (shoulder, 17700), IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2200 (CN); 1642 (C=O), besides 3,4-dioxohexahydroindole derivative **44**, mp 217–221°, UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (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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Received June 22, 1973