Enamides (41). Carbinolamide **39** was intimately ground with anhydrous $MgSO_4$ and the powdered mixture was sublimed at 70–105° (0.1–0.15 mm). After two such sublimations a quantitative yield of the mixture of enamides was obtained. Thin layer analysis showed only the slightest difference in R_f for these two substances employing a number of solvents and solvent systems; consequently preparative separation was not attempted. The mixture was recrystallized from benzene: mp 110–113° with softening at 107°; ir (Nujol) 3200, 1710, 1670, 1650 cm^{-1}; pmr 4.90, 4.37, 4.10 (multiplets), 2.55 (t), 1.91 (d), 1.23 and 1.18 (s); mass spectrum, calcd mol wt, 125.17; found, 125.

Anal. Calcd for $C_7H_{11}NO$: C, 67.2; H, 8.8; N, 11.2. Found: C, 67.1; H, 9.0; N, 11.2.

β-Cyano Ketone (44). To a solution of the "combination" hydrocyanation reagent[29] (prepared from 129.5 g of 25% Et_3Al in toluene and 9 ml of HCN) was added dropwise with stirring and cooling in ice 27 g of cyclopentenone **43** over 30 min. The solution was stirred for 1 hr in the cold and then 2.5 hr at room temperature. The mixture was then poured in portions into a 10% KOH solution (200 ml) containing crushed ice. The organic layer was separated and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried over K_2CO_3 and freed of solvent. The product distilled as a colorless oil: bp 73–74° (0.2 mm); 15 g (46%); ir (neat) 2250, 1735 cm^{-1}; pmr δ 1.53 and 1.43 (s, 3 H each).

Anal. Calcd for C_9H_3NO: C, 71.5; H, 8.6. Found: C, 71.7; H, 8.9.

Carbinolamide (45). β-Cyano ketone **44** (10.67 g) was refluxed in 25 ml of $NaHCO_3$–Na_2CO_3 pH 10 aqueous buffer and 13 ml of EtOH for 11 hr. The volume was reduced *in vacuo*, diluted with H_2O, and extracted with $CHCl_3$, and the extracts were dried over $MgSO_4$. Evaporation of the solvent left a yellow gum which produced a white solid when triturated with ether–ethyl acetate. Recrystallization from ethyl acetate gave 7.2 g (60%) of colorless crystals: mp 117.5–118.5°; ir (Nujol) 3380, 3220, 1670 cm^{-1}; pmr δ 7.47 (bs, 1 H), 5.0 (s, 1 H), 1.35 and 1.10 (s, 3 H each); mass spectrum, calcd mol wt, 169.22; found, 169.

Anal. Calcd for $C_9H_{15}NO_2$: C, 64.0; H, 8.9; N, 8.3. Found: C, 64.0; H, 9.0; N, 8.1.

Dimers 46 and 48. To a hot solution of KO-*tert*-Bu in *tert*-BuOH (prepared by dissolving 0.57 g of K in 25 ml of *tert*-BuOH) was added nitrile **40** (1.13 g) and the mixture was refluxed under N_2 for 5 hr. The solution was cooled and partitioned between chloroform and brine. The organic extracts were dried ($MgSO_4$) and the solvent was evaporated leaving a pale-yellow gum which crystallized upon trituration with EtOH. Recrystallization from aqueous EtOH gave dimer **46** (0.294 g) as colorless cubes: mp 192–194°; uv λ_{max} 232 nm (ε 11,600); ir (Nujol) 3200, 3090, 1720, 1670 cm^{-1}; pmr δ 9.0, 7.95 (broad s, 1 H each), 4.49 (t, 1 H), 2.46 (d, 2 H), 2.00 (d, 2 H), 1.40 (s, 3 H), *ca.* 1.2 (multiplet, 4 × 3 H); mass spectrum, calcd mol wt, 236.3; found, 236.

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.2; H, 8.8; N, 11.2. Found: C, 66.9; H, 8.9; N, 11.3.

The mother liquors were evaporated to dryness and the residue was tritiated with Et_2O. This yielded a white solid consisting of a mixture of **46** and **48** which was separated by column chromatography using neutral alumina (act. II). Dimer **48** was obtained as white crystals from ethyl acetate–methanol: mp 183–184°; uv λ_{max} 255 nm; ir (Nujol) 3210, 3090, 1690 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.2; H, 8.8; N, 11.2. Found: C, 67.2; H, 9.0; N, 10.9.

Catalytic hydrogenation of **46** and **47** converted each substance into the same two stereoisomeric reduction products, confirming their isomeric nature.

Acknowledgments. The authors are grateful to the National Science Foundation (GP-11312), The Robert A. Welch Foundation, the A. P. Sloan Foundation, and Eli Lilly Co. for financial support. The nmr and mass spectrometers employed in this study were purchased with funds provided by the National Science Foundation.

Studies on the Synthesis of Corrins and Related Ligands. II. The Employment of Isoxazoles in the Synthesis of Semicorrins[1]

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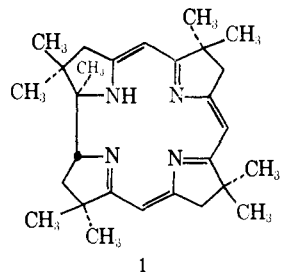
Contribution from the Department of Chemistry, Rice University, Houston, Texas 77001. *Received February 24, 1971*

Abstract: A new, quite versatile, method for the synthesis of semicorrins is described which is based on the special utility of isoxazoles as intermediates.

The model studies disclosed in the preceding paper[6a] now allow us to more clearly define an actual corrin synthesis. Let us, therefore, refocus our attention on octamethylcorrin (**1**). In this connection mention should be made of the fact that the details of corrin biosynthesis remain obscure. However, from a strictly chemical point of view, Eschenmoser[6b] has made the intriguing suggestion that the so-called "corphin" ligand may play a role in this process. Although as yet undetected in nature, the



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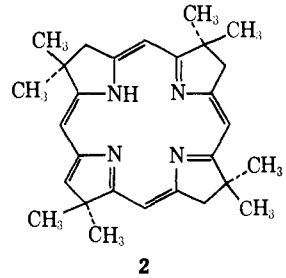

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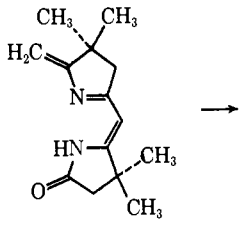
(1) Preliminary communications: R. V. Stevens, L. E. DuPree, Jr., and M. P. Wentland, *Chem. Commun.*, 821 (1970).
(2) A. P. Sloan Fellow, 1969–1971.
(3) NSF Predoctoral Trainee, 1966–1970.
(4) NSF Predoctoral Fellow, 1969–present.
(5) U. S. Public Health Service Predoctoral Fellow, 1967–1970.
(6) (a) R. V. Stevens, C. G. Christensen, W. L. Edmonson, M. Kaplan, E. B. Reid, and M. P. Wentland, *J. Amer. Chem. Soc.*, **93**, 6629 (1971); (b) A. P. Johnson, P. Wehrli, R. Fletcher, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 7, 623 (1968).

corphin system, *e.g.*, **2**, differs from a corrin ligand, *e.g.*,**1**, by only a reductive ring contraction. Therefore, octamethylcorphin (**2**) becomes an interesting additional target of our synthetic studies.

Our initial objective in corrin or corphin synthesis was to test the feasibility of employing isoxazoles as a reliable and efficient method of synthesizing semicorrins **3** and **4**. This goal was dictated by the fact that Eschenmoser[7] had previously incorporated semicorrin **3** into various corrin complexes **5**. The ingenious use of various transition metal elements as templates played an important role in this outstanding achievement. In a related study[6b] this same semicorrin, **3**, served as both halves of the symmetrically substituted octamethylcorphin–palladium complex **6**. The possibility of employing the alternative semicorrin **4** in both of these processes also captured our imagination.



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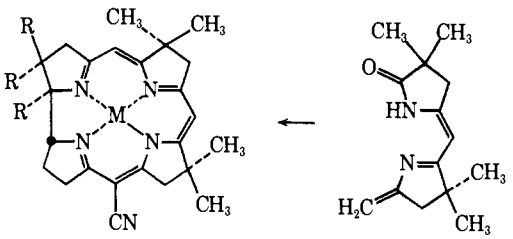

5, M = Ni, Pd^{+}, Co(CN); M ≠ Zn^{+}, Li, Na

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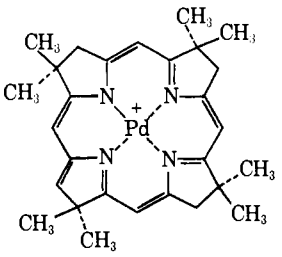

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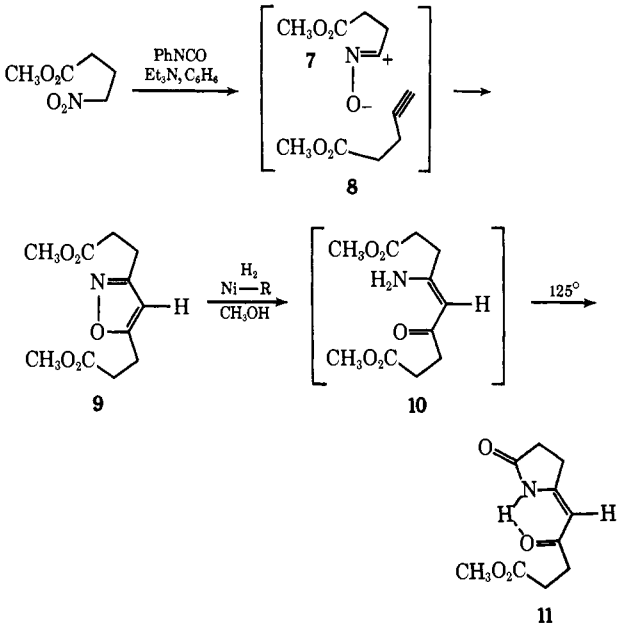
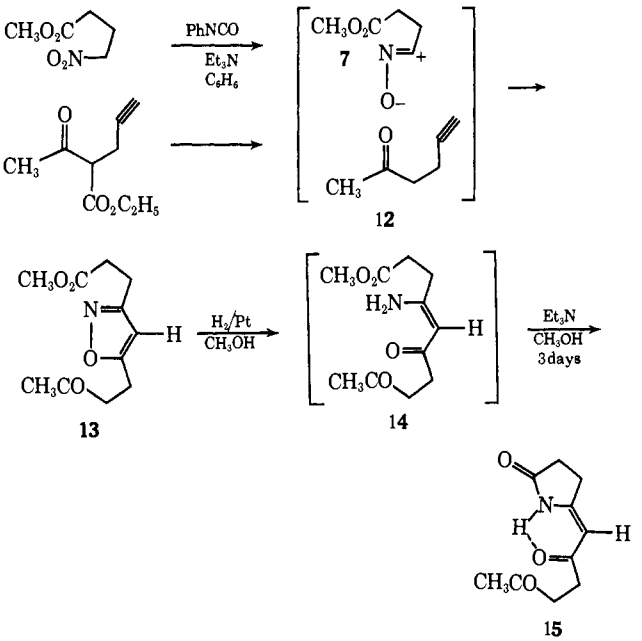
Thus far in our study we have determined the feasibility of employing a number of diversely substituted nitrile oxides in the cycloaddition step. Armed with these encouraging results our attention naturally turned to the acetylenic partner. Once again substrates and products were carefully selected to include certain features which we felt would be useful in more precisely defining an actual corrin synthesis.

Thus, cycloaddition of the previously employed nitrile oxide **7** and acetylenic ester **8** afforded isoxazole **9** in 53% yield. Reduction of this particular isoxazole was best achieved by means of Raney nickel catalyst in methanol. The resultant vinylogous amide, **10**, could be identified spectroscopically in the reaction mixture, but no attempt was made to isolate and purify this substance since spontaneous cyclization could be induced by pyrolysis. In this manner analytically pure **11** could readily be secured in 64–74% yield overall from isoxazole **9**.



8 **9** **10** **11**

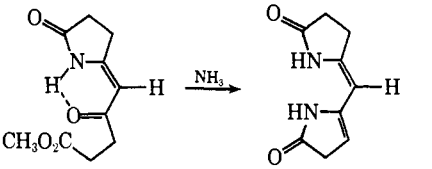
Similarly, cycloaddition of this nitrile oxide, **7**, and acetylenic ketone **12** provided a 50% yield of isoxazole **13**. Quantitative reduction of this intermediate was achieved by employing a platinum catalyst in methanol solution. Once again the vinylogous amide **14** could readily be identified spectroscopically in the reduction mixture but was not isolated. In contrast to amino ester **10** pyrolytic cycloelimination of the elements of methanol from **14** could not be effected without extensive decomposition, and an alternative method had to be devised. After some experimentation, nicely crystalline lactam **15** was finally secured, albeit in modest yield, by simply adding a catalytic amount of triethylamine base to a methanolic solution of **14** and allowing the mixture to stand at room temperature for 3 days.

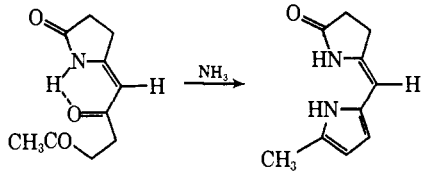


12 **13** **14** **15**

(7) A. Eschenmoser, *Quart. Rev., Chem. Soc.*, **24**, 366 (1970), and references cited therein.

Prior to their preparation, we had anticipated that upon exposure to ammonia keto ester **11** would yield the simple semicorrin **16** (or a tautomeric equivalent thereof). Similarly, diketone **15** was expected to provide **17**. However, attempts to achieve these transformations have uniformly failed thus far. For example, keto ester **11** proved to be a surprisingly inert substance and could be recovered unscathed when treated with ammonia (or one of its equivalents) under a variety of standard conditions. It was, therefore, clear that in future experiments we could not rely on such a system as a means for introducing one of the required rings of the corrin ligand. On the other hand, the problem of employing diketone **15** was not one of lack of reactivity. On the contrary, treatment of this substance with a saturated methanolic ammonia solution at 0° yielded a viscous dark brown oil which contained little, if any, starting material. From spectral data it was equally clear that **17** is at best a very minor component of the complex product mixture.[8] Although negative, these results were nevertheless informative in the design and execution of subsequent experiments.

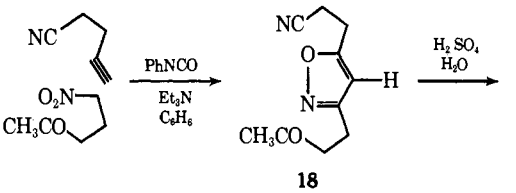


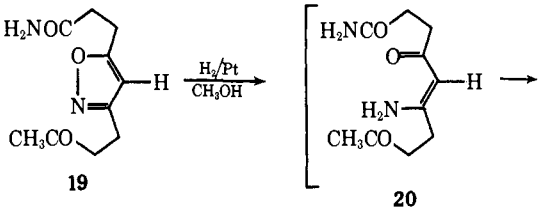


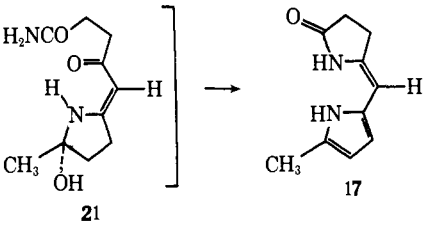
The failure of keto ester **11** to undergo an intermolecular reaction with ammonia was of some concern with regard to our subsequent plans and prompted further consideration of alternative means of achieving this result. In this connection, the possibility of altering the structure of our intermediates in such a way that this crucial synthetic step could be achieved by an intra- rather than an intermolecular operation presented itself as a logical solution to what is, in fact, a common problem in organic synthesis. Isoxazole **18** was, therefore, prepared in the standard way and converted to the corresponding amide, **19**, in high yield. Reduction of this substance proceeded without incidence *via* **20** to the expected vinylogous carbinolamide **21**. Not surprisingly **21** proved to be a very labile substance. Indeed, it is completely decomposed to unidentified products in as little as 2 hr upon exposure to the air. However, we are confident of its identity from both its pmr spectrum and the fact that a freshly prepared sample exhibits the correct parent ion.

As a consequence of its instability **21** had to be utilized immediately. Therefore, a freshly prepared sample was added to an excess of potassium *tert*-butoxide in *tert*-butyl alcohol and the resultant solution

(8) G. Traverso, A. Barco, G. P. Pollini, M. Anastasia, V. Sticchi, and D. Pirillo (*Farmaco, Ed. Sci.*, 24, 946 (1969)) have reported the successful conversion of **15** into **17**. However, the yield was not specified.







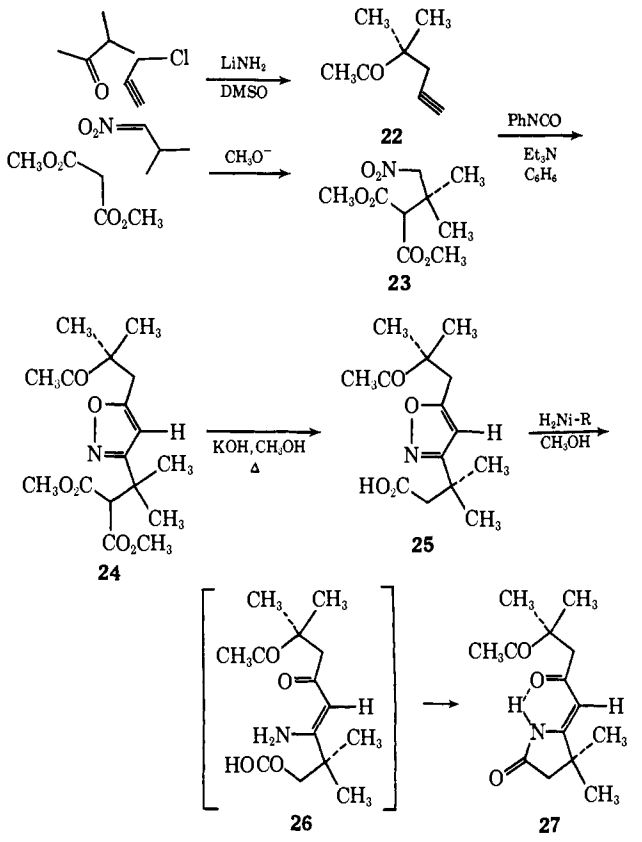
was refluxed under nitrogen. After extensive purification a very small amount of an unstable light yellow solid was obtained whose pmr and mass spectral features were consistent with structure **17**. Although by no means the synthetic triumph we had hoped for, the results of these experiments were sufficiently encouraging to warrant further application later in our study (see **34** and discussion).

With these results in hand we turned our attention to the synthesis of semicorrins **3** and **4**. The isoxazole scaffold **25**, destined to become semicorrin **3**, was obtained in the now standard manner. The required acetylenic ketone **22** was prepared in a single step in 25% yield from the lithium amide induced alkylation of isopropyl methyl ketone, with propargyl chloride under carefully defined conditions. The nitro diester **23** was prepared by conjugate addition of dimethyl malonate to 1-nitroisobutene using the method described for diethyl malonate.[9] The dehydration of this substance was best achieved *in situ* by slow addition of a mixture of the nitro compound and triethylamine to a benzene solution of the acetylene and phenyl isocyanate. When executed in this manner a 95% yield of isoxazole **24** was obtained. Saponification and decarboxylation yielded keto acid **25**. Hydrogenation of this isoxazole over Raney nickel catalyst yielded vinylogous amide **26** which could be detected spectroscopically. However, by simply allowing the methanolic solution to stand over the basic catalyst spontaneous ring closure occurred. We were somewhat surprised by the apparent ease of this cyclization, but in any event it was a pleasant surprise indeed.

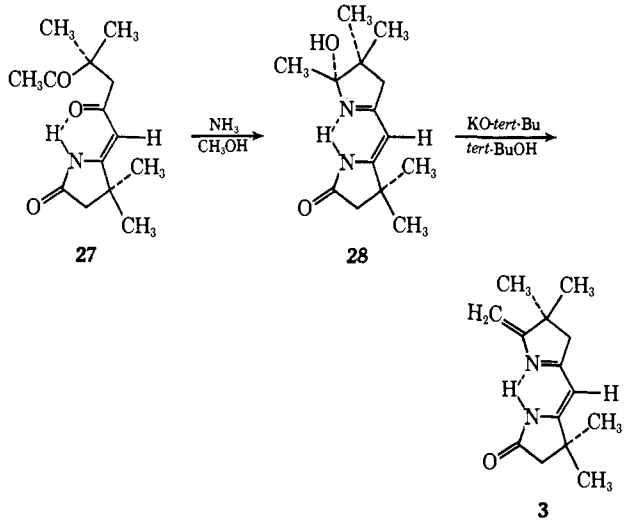
Vinylogous amide **27** had been previously prepared by Eschenmoser[10] and converted into semicorrin **3**. Thus, exposure of diketone **27** to a saturated methanolic solution of ammonia yielded the vinylogous amidine chromophore **28** without any difficulty (compare

(9) C. Bahner, U. S. Patent 2,431,451 (1947); *Chem. Abstr.*, **42**, 2615 (1948).

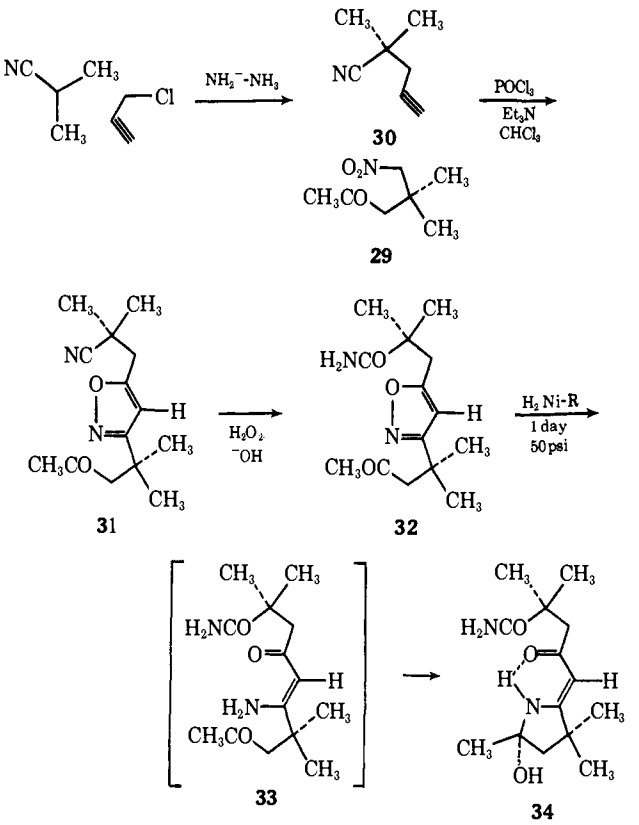
(10) E. Bertole, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gripi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem., Int. Ed. Engl.*, 3, 490 (1964).



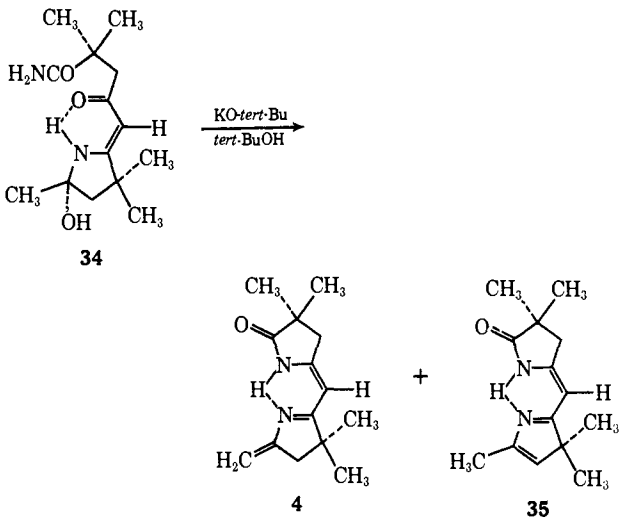
this result to the unsubstituted simple model **15**). Subsequent potassium *tert*-butoxide induced dehydration of this substance yielded the desired semicorrin **3** identical in all respects with the Eschenmoser compound.



Synthesis of alternative semicorrin **4** was accomplished in an analogous fashion. Thus, lithium amide induced alkylation[11] of isobutyronitrile with propargyl chloride provided the acetylenic nitrile **30**. Dehydration of nitro ketone **29**[12] was accomplished by means of phosphorous oxychloride and triethylamine base in chloroform.[13] The reaction proceeded smoothly and a 43% yield of the desired isoxazole **31** was obtained. Alkaline hydrogen peroxide hydrolysis[14] of this nitrile function quantitatively yielded the highly crystalline amide **32** whose subsequent hydrogenolysis provided vinylogous carbinolamide **34** in essentially quantitative yield.



In contrast to the unsubstituted model **21**, cycloelimination of 2 equiv of water from **34** was easily achieved in 90% yield by exposure to 2 equiv of KO-*tert*-Bu in boiling *tert*-BuOH. The crude product was conveniently purified by sublimation, and the resultant green-yellow needles appeared homogeneous by tlc using a number of solvent systems. However, spectral analysis revealed the presence of the two tautomeric



(11) According to the procedure of M. Minssen-Guette and J. Jacques, *Bull. Soc. Chim. Fr.*, 2105 (1968).

(12) L. I. Smith and V. A. Englehardt, *J. Amer. Chem. Soc.*, 71, 2676 (1949).

(13) A slight modification of the procedure of G. B. Bachman and L. E. Strom (*J. Org. Chem.*, 28, 1150 (1963)) was employed.

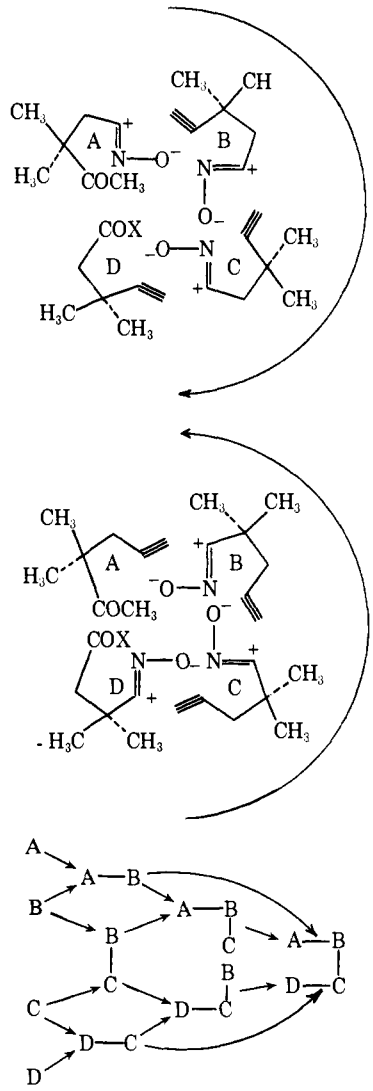
(14) R. Q. Brewster and W. Schroeder, "Organic Syntheses," Collect. Vol. 2, Wiley, New York, N. Y., 1943, p 586.

semicorrins **4** and **35** in an approximate ratio of 1:3.5. Attempts to effect the separation of **4** and **35** have been uniformly unsuccessful.

Construction of the Macrocyclic Ligand

As mentioned in the previous paper,[6a] we had considered very early in our investigation the possibility of incorporating more than one isoxazole scaffold into the same molecule as a means of establishing a network of ring-bridging vinylogous amidine chromophores.

In principle, all of the structural features of octamethylcorrin (**1**) (or octamethylcorphin (**2**)) can be incorporated into an appropriately substituted triisoxazole system which, in turn, could be elaborated from carefully selected nitrile oxides and terminal acetylenes in either of the two modes suggested by the following diagram, *i.e.*, either in a clockwise or counterclockwise fashion. Within each mode these combinations could be executed in a variety of ways as illustrated. The possibilities pregnant in this particular approach are actively being pursued.



Experimental Section[15]

3,5-(2-Carbomethoxyethyl)isoxazole (9). Methyl-4-nitrobutyrate (1.31 g, 8.9 mmol) and methyl-4-pentynoate (1.5 g, 13.4 mmol) were placed in a flask equipped with condenser, N_2 inlet, and magnetic stirrer. Dry benzene (90 ml), 2.92 g of phenyl isocyanate, and several drops of freshly distilled Et_3N were added and the mixture was stirred at room temperature for 96 hr. It was then cooled to 0° and the precipitated diphenylurea removed by filtration. The solvent was removed *in vacuo* and the residue was chromotographed on silica gel. Recrystallization from hexane gave 1.13 g (53%) of isoxazole **9**: mp 58.5–59.5°; ir ($CHCl_3$) 1735, 1605 cm^{-1}; pmr δ 5.95 (s, 1 H), 3.75 (s, 6 H), *ca.* 2.9 (m, 8 H).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.9; H, 6.24; N, 5.81. Found: C, 54.9; H, 6.22; N, 5.69.

Vinylogous Amide 11. Isoxazole **9** was reduced at atmospheric pressure in methanol solvent in the presence of a trace of Et_3N. After uptake of H_2 ceased, the catalyst was removed by filtration and the filtrate was freed of solvent leaving a light yellow oil which was placed in a "Kugelröhr" apparatus and heated *in vacuo* at 120° for 24 hr. This provided at 74% yield of **11**, mp 108–110°. Resublimation (105–110° (0.1 mm)) afforded analytically pure crystals: ir (KBr) 3290, 1730, 1660, 1595 cm^{-1}; pmr δ 5.5 (t, 1 H), 3.75 (s, 3 H), *ca.* 2.7 (m, 8 H); uv 286 nm (ϵ 16,000).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.16. Found: C, 56.78; H, 6.35.

3-(2-Carbomethoxyethyl)-5-(3-oxobutyl)isoxazole (13). Methyl-4-nitrobutanoate (0.74 g, 5 mmol), 5-hexyn-2-one[16] (0.72 g, 7.5 mmol), 1.5 ml (14 mmol) of phenyl isocyanate, and 50 ml of dry benzene were combined and then several drops of freshly distilled Et_3N were added. The mixture was stirred at room temperature for 4 days, then the precipitated diphenylurea was removed by filtration. The filtrate was concentrated and the residue was chromatographed on silica gel which provided 1.0 g (80%) of reasonably pure isoxazole **13**: ir (neat) 1735, 1710, 1605 cm^{-1}; pmr δ 5.95 (s, 1 H), 3.75 (s, 3 H), 3.13–2.52 (m, 8 H), 2.20 (s, 3 H); mass spectrum, calcd mol wt, 225.2; found, 225.

The yellow 2,4-dinitrophenylhydrazone of **13** was prepared: mp 127–127.5° (95% EtOH); mass spectrum, calcd mol wt, 405.4; found, 405.

Anal. (2,4-DNP) Calcd for $C_{17}H_{19}N_5O_7$: C, 50.37; H, 4.72. Found: C, 50.10; H, 4.89.

Vinylogous Amide 15. Reduction of **13** proceeded smoothly and quantitatively in methanol solvent over PtO_2 (Adams catalyst). Removal of the catalyst and evaporation of the solvent provided the open-chain vinylogous amide **14** as a colorless oil which rapidly darkens upon exposure to the air: pmr δ 5.15 (s, 1 H), 3.80 (s, 3 H), 2.83–250 (m, 8 H), 2.24 (s, 3 H).

The crude reduction product was immediately dissolved in CH_3OH and a small amount of freshly distilled Et_3N was added. The reaction was sealed under N_2, allowed to stand for 45 hr, and then concentrated under reduced pressure and the residue chromatographed on silica gel. Recrystallization from CCl_4 provided white needles of **15**: mp 79–81° (20%); ir ($CHCl_3$) 1740, 1713, 1655, and 1585 cm^{-1}; uv max 280 nm (ϵ 14,800); pmr δ *ca.* 11.0–9.5 (v broad, 1 H), 5.60 (t, 1 H), 3.10–2.36 (m, 8 H), 2.25 (s, 3 H); mass spectrum, calcd mol wt, 195.2; found, 195.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71. Found: C, 61.36; H, 6.84.

3-(3-Oxobutyl)-5-(2-cyanoethyl)isoxazole (18). To a mixture of 0.66 g (5 mmol) of 5-nitro-2-pentanone,[17] 0.60 g (7.5 mmol) of 4-cyanobut-1-yne,[18] and 1.5 ml (13.9 mmol) of phenyl isocyanate in 50 ml of dry benzene were added several drops of freshly distilled (from $LiAlH_4$) Et_3N. The reaction was stirred at room temperature for 4 days; then the precipitated diphenylurea was filtered off. The filtrate was concentrated under reduced pressure and the residue was chromatographed on a silica gel column from which 0.87 g (90%) of reasonably pure isoxazole was obtained. Further purification can be achieved by vacuum distillation in a "Kugelröhr" apparatus: ir (neat) 2250, 1715, and 1605 cm^{-1}; pmr δ 6.08 (s, 1 H), 3.26–2.55

(15) Infrared spectra were secured on a Beckman IR-8 spectrophotometer; ultraviolet spectra are of 95% ethanol solutions and were recorded on a Cary Model 14 or Bausch and Lomb Spectronic 505 spectrometer. Proton magnetic resonance (pmr) spectra were recorded in dilute deuteriochloroform solutions (unless indicated otherwise) containing tetramethylsilane as internal standard on a Varian A-56/60A spectrometer operating at 60 MHz. Melting and boiling points are uncorrected. Microanalyses were secured from the Elek Microanalytical Laboratory, Torrence, Calif. Preparative and thin layer chromatography operations employed Brinkmann precoated plates of silica gel F-254.

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(m, 8 H), 2.20 (s, 3 H). Analytical data were secured on the corresponding (crystalline) amide **19** (which see).

3-(3-Oxobutyl)-5-(2-carboaminoethyl)isoxazole (19). To 0.3 g (1.56 mmol) of cyano ketone **18** was added 1.2 ml of concentrated (96%) H_2SO_4. The stirred solution was warmed to 80–85° and maintained at that temperature for 5 min, then cooled and poured into a cold 6 *N* NaOH solution, the amount of which was adjusted so that a basic aqueous phase results. The aqueous solution was then extracted continuously with CH_2Cl_2 and the organic extracts were dried over Na_2SO_4 and freed of solvent. Recrystallization from benzene–methanol gives 0.28 g (85%) of beautiful white crystals of amide **19**: mp 135–136°; ir (Nujol) 1715, 1650, and 1605 cm^{-1}; pmr δ 6.08 (s, 1 H), 3.10–2.45 (m, 8 H), 2.18 (s, 3 H); mass spectrum, calcd mol wt, 210.2; found, 210.

Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71. Found: C, 57.16; H, 6.86.

4,4-Dimethyl-5-oxo-hex-1-yne (22). Approximately 500 ml of commercial anhydrous ammonia was condensed into a flame-dried flask equipped with mechanical stirrer, N_2 blanket, Dry Ice condenser, and a gas inlet. Lithium amide was generated using 6.94 g (1 mol) of freshly cut Li and a catalytic amount of $FeCl_3$. Methyl isopropyl ketone (86 g, 1 mol dried over type 4A molecular sieves) was added dropwise to the refluxing slurry. The mixture was stirred for 2 hr and the NH_3 was allowed to evaporate. The resultant salt was warmed to 50° and the vessel flushed with N_2 to remove as much residual NH_3 as possible. Approximately 400 ml of dry DMSO was added and the dark slurry was cooled to *ca.* 10°; 82 g (1.1 mol) of propargyl chloride was added at such a rate that the temperature could be maintained at less than 15°. After addition was complete the mixture was allowed to warm to room temperature and stirred for an additional 6 hr and then poured into 1 l. of H_2O and acidified with acetic acid. The solution was extracted with three 150-ml portions of benzene which were combined, washed with brine, dried ($MgSO_4$), and concentrated to *ca.* 200 ml. This concentrate is then flash distilled to give 50–60 ml of a DMSO–propargyl chloride–product mixture, to which 1 g of hydroquinone was added, and the mixture was fractionated through a short Vigreux column to provide 33.7 g (27%) of **22** as a clear liquid: bp 74–76° (34 mm); ir (neat) 3300, 2110, 1710 cm^{-1}; pmr δ 1.25 (s, 6 H), 2.0 (t, 1 H), 2.2 (s, 3 H), 2.4 (d, 2 H). The ketone was analyzed as its 2,4-DNP derivative: mp 112–112.5°.

Anal. Calcd for $C_{14}H_{16}O_4N_4$: C, 55.26; H, 5.30. Found: C, 55.15; H, 5.54.

Nitro diester (23) was prepared according to the same procedure described by Bahner[19] for the corresponding diethyl ester: bp (dimethyl ester) 110–111° (0.38 mm); ir (neat) 1735, 1549, 1378 cm^{-1}; pmr δ 1.27 (s, 6 H), 3.65 (s, 1 H), 3.76 (s, 6 H), 4.70 (s, 2 H).

Isoxazole 24. Acetylenic ketone **22** (4 g, 32 mmol) and phenyl isocyanate (3.1 g, 26 mmol) were combined in 5 ml of dry benzene under N_2. Nitro diester **23** (3 g, 13 mmol), and 2 ml of freshly distilled Et_3N were combined in 50 ml of dry benzene and added dropwise to the mixture of **22** and phenyl isocyanate at a rate of *ca.* 1 ml/hr. After addition was complete the mixture was stirred an additional 24 hr; then the precipitated diphenylurea was removed by filtration. The solvent was removed under reduced pressure and excess **22** was recovered by distillation. The pot residue was dissolved in $CHCl_3$, washed with water, and filtered to give a brown oil which was filtered through a short silica gel column to remove the discoloration. Pmr analysis of the resultant oil revealed that it was sufficiently pure isoxazole to proceed to the next step. An analytical sample was secured by preparative layer chromatography: ir (neat) 1760, 1735, 1708, 1600 cm^{-1}; pmr δ 1.2 (s, 6 H), 1.52 (s, 6 H), 2.16 (s, 3 H), 2.95 (s, 2 H), 3.68 (s, 6 H), 3.92 (s, 1 H), 5.93 (s, 1 H); mass spectrum, calcd mol wt, 339.4; found, 339.

Anal. Calcd for $C_{17}H_{25}O_6N$: C, 60.16; H, 7.42. Found: C, 59.86; H, 7.52.

Isoxazole 25. The crude isoxazole **24** (3.05 g, 9 mmol) obtained in the previous step was refluxed for 4 hr in a solution of 30 ml of CH_3OH in which 5 g of KOH had been dissolved. The reaction was then cooled, diluted with 70 ml of H_2O, extracted twice with ether, and acidified with HCl. The resultant emulsion was extracted continuously with $CHCl_3$; then the $CHCl_3$ extract was dried ($MgSO_4$) and freed of solvent to provide a viscous oil which pmr analysis identified as a very clean mixture of di- and monoacids. Decarboxylation was completed by boiling in toluene and the acid was extracted into the minimum amount of 10% NaOH solution. The water was removed *in vacuo* and the resultant semisolid salt was neutralized with the minimum amount of 15% HCl and extracted with three 50-ml portions of $CHCl_3$ thus providing 1.75 g (73%) of oily **25** whose pmr spectrum demonstrated to be sufficiently pure for the reductive step. Analytical data were secured on the corresponding methyl ester which was easily purified by preparative layer chromatography: ir (neat) 3200 (b), 1705, 1600 cm^{-1}; pmr δ 1.20 (s, 6 H), 1.42 (s, 6 H), 2.17 (s, 3 H), 2.66 (s, 2 H), 2.96 (s, 2 H), 3.6 (s, 3 H), 5.90 (s, 1 H); mass spectrum, calcd mol wt, 281.3; found, 281.

Anal. Calcd for $C_{15}H_{23}O_4N$: C, 64.04; H, 8.24. Found: C, 63.98; H, 8.37.

Vinylogous Amide 27. Isoxazole monoacid **25** (1.03 g, 3.85 mmol) was dissolved in 10 ml of CH_3OH and a spatula of no. 28 Active Raney Nickel catalyst was added and reduced at 25° under 1 atm of H_2. After reduction was complete, the mixture was stirred overnight to complete ring closure after which the pale green solution was treated with H_2S and filtered. Concentration of the filtrate provided a gray-green gum which pmr analysis shows to be 80–90% **27**. Purification by preparative layer chromatography yields an oil which solidifies to off-white crystals when triturated with ether. Recrystallization from benzene–ether gave crystals whose spectral features were identical with those described by Eschenmoser:[10] ir ($CHCl_3$) 3300, 1750, 1705, 1660, 1585 cm^{-1}; uv 203 (ϵ 7410), 282 nm (ϵ 20,400); pmr δ 1.20 (s, 6 H), 1.31 (s, 6 H), 2.16 (s, 3 H), 2.29 (s, 2 H), 2.74 (s, 2 H), 5.30 (s, 1 H), 10.45 (broad s, 1 H); mass spectrum, calcd mol wt, 251.3; found, 251.

Carbinolamine (28). The procedure is essentially that of Eschenmoser.[10] Lactam diketone **27** (350 mg, 1.39 mmol) was dissolved in 15 ml of anhydrous CH_3OH and an approximately equal amount of commercial anhydrous ammonia condensed into the flask under N_2. The mixture was allowed to warm to room temperature and when NH_3 evolution had become quite slow the flask was tightly stoppered and allowed to stand for 4 days at room temperature; then the solvent and excess NH_3 were evaporated under a stream of N_2 to give a creamy white solid which pmr analysis revealed was *ca.* 80% **28** and a trace of starting material. Recrystallization from ether–benzene provided a white solid, mp 151–152.5°. Two more recrystallizations with drying *in vacuo* at room temperature (**28** seems to be fairly heat sensitive) gave clusters of fat needles, mp 169–171°, in a vacuum sealed capillary. All spectral data were in good agreement with the published values:[10] ir ($CHCl_3$) 3600, 1735 (sh), 1720, 1650, 1595 cm^{-1}; uv 204 (ϵ 15,120), 284 (ϵ 9770), 347 nm (ϵ 24,000); pmr δ 1.02 (s, 3 H), 1.10 (s, 3 H), 1.30 (s, 3 H), 1.39 (s, 3 H), 2.32 (d, 1 H, J = 16 Hz), 2.35 (s, 2 H), 2.71 (d, 1 H, J = 16 Hz), 4.95 (s, 1 H), 5.90 (s, 2 H); mass spectrum, calcd mol wt; 250.3; found, 250.

Semicorrin (3). The procedure is essentially that of Eschenmoser.[10] Carbinolamine **28** (70 mg, 0.28 mmol) was taken up in 10 ml of dry *tert*-BuOH and placed under an N_2 atmosphere. Potassium *tert*-butoxide in *tert*-BuOH (0.31 mmol) was syringed into the reaction vessel and the mixture was brought to a gentle reflux and maintained for 2.5 hr. The mixture was then poured into H_2O and extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to provide 58 mg (89%) of crude **3**. Three recrystallizations from CH_2Cl–hexane and one from hexane gave fine, white needles of mp 152.5–154° with sintering at 142°. All spectral data agreed with published values:[10] ir ($CHCl_3$) 3160, 1740 (sh), 1720, 1640, 1595 cm^{-1}; uv 207 (ϵ 13,490), 220 (sh, ϵ 12,000), 252 (ϵ 8510), 261 (ϵ 890), 272 (ϵ 8510), 323 (ϵ 14,470), *ca.* 337 (sh, ϵ 13,800), *ca.* 371 nm (sh, ϵ 8320); pmr δ 1.18 (s, 6 H), 1.33 (s, 6 H), 2.38 (s, 2 H), 2.59 (s, 2 H), 4.51, (s, 1 H), 5.03 (s, 1 H), 5.06 (s, 1 H); mass spectrum, calcd mol wt, 232.3; found, 232.

4-Cyano-4-methyl-1-pentyne (30). This nitrile was prepared by a procedure similar to that of Minsson-Guelte.[11] A solution of $LiNH_2$ in liquid NH_3 was prepared by dissolving 1.74 g (0.25 mol) of Li metal in 250 ml of liquid NH_3 in the presence of a catalytic amount of ferric nitrate. To this gray slurry was added 17.25 g (0.25 mol) of isopropyl cyanide over a 2-min period (a Dry Ice–acetone bath and condenser were employed). A color change of the slurry to green was noted. Then 24.3 g (0.32 mol) of propargyl chloride was added rapidly (*ca.* 30 sec) resulting in a vigorous reaction and immediate brown color. This mass was stirred for an additional 30 min when 15 g of NH_4Cl and 125 ml of "wet ether" were added. External cooling was removed and the black slurry allowed to warm to room temperature. The ethereal slurry was filtered to remove resinous materials and inorganic salts, washed twice with water, dried ($MgSO_4$), and concentrated to provide a deep red viscous oil. Vacuum distillation provided 5.3 g (20%) of pure nitrile **30**: bp 48–50° (14 nm); ir (neat) 3300 and 2240 cm^{-1}; pmr δ 2.49 (d, 2 H, J = 2.8 Hz), 2.19 (t, 1 H, J = 2.8 Hz),

(19) C. T. Bahner, *Chem. Abstr.*, **42**, 2615 (1948).

1.47 (s, 6 H). This nitrile was analyzed as its crystalline amide prepared by alkaline hydrogen peroxide hydrolysis: mp 87–87.5° (hexane–benzene); ir ($CHCl_3$) 3540–3275 (multiplet), 2110, 1670, and 1586 cm^{-1}; pmr δ 2.38 (d, 2 H J = 2.8 Hz), 2.07 (t, 1 H, J = 2.8 Hz), 1.27 (s, 6 H); mass spectrum, calcd mol wt, 125.2; found, 125.

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.89; N, 11.19. Found: C, 67.37; H, 8.92; N, 11.14.

Isoxazole 31. A slight modification of the procedure of Bachmann[20] was employed. Nitro ketone **29**[21] (9.5 g, 0.06 mol), acetylenic nitrile **30** (6.4 g, 0.06 mol), 36.2 g (0.36 mol) of triethylamine (freshly distilled from CaH_2), and 200 ml of dry $CHCl_3$ were charged into an N_2-purged flask. Phosphorous oxychloride (11.9 g, 0.078 mol) was added dropwise at room temperature with stirring resulting in the evolution of HCl and an immediate darkening of the solution to deep red. The mixture was refluxed for 48 hr and then concentrated under reduced pressure. The dark oily residue was taken up in ether, washed with four portions of H_2O, twice with dilute HCl, once with dilute $NaHCO_3$, dried ($MgSO_4$), and concentrated. The resulting red oil was vacuum distilled yielding 6.29 g (42%) of the desired isoxazole **31**: bp 135–138° (0.14 mm); ir (neat) 3122, 2240, 1714, and 1603 cm^{-1}; pmr δ 6.25 (s, 1 H), 3.02 (s, 2 H), 2.87 (s, 2 H), 2.09 (s, 3 H), 1.45 (s, 12 H); mass spectrum, calcd mol wt, 248.3; found, 248.

A 2,4-DNPH derivative melted at 139.5–140°.

Anal. Calcd for $C_{20}H_{24}N_6O_5$: C, 56.06; H, 5.65; N, 19.62. Found: C, 56.01; H, 5.79; N, 19.43.

Isoxazole 32. A procedure similar to that of Brewster[22] was employed. Isoxazole **31** (2.0 g), 5 ml of 30% H_2O_2, 0.7 ml of 6 N NaOH, and 25 ml of ethanol were stirred at 50° for 7 hr. The excess H_2O_2 was destroyed with a small amount of Pd/C until O_2 evolution ceased. The slurry was filtered and concentrated leaving a white crystalline mass which was dissolved in ether, washed with water, dried ($MgSO_4$), and concentrated yielding 2.0 g (98%) of white crystals. Analytically pure isoxazole was recrystallized from hexane–benzene: mp 92–93°; ir ($CHCl_3$) 3520, 3420, 3180 (broad), 1714, 1672, and 1598 cm^{-1}; pmr δ 6.25 (broad s, 2 H), 6.03 (s, 1 H), 3.00 (s, 2 H), 2.83 (s, 2 H), 2.07 (s, 3 H), 1.40 (s, 6 H), 1.27 (s, 6 H); mass spectrum, calcd mol wt, 266.3; found, 266.

Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.33; N, 10.52. Found: C, 63.04; H, 8.43; N, 10.52.

Carbinolamide (34). Isoxazole **32** (1.0 g, 3.8 mmol) was dissolved in 100 ml of ethanol and 2 teaspoonsful of no. 28 active Raney nickel catalyst was added. This slurry was hydrogenated in a Parr apparatus for 24 hr at 40 psi of H_2. The catalyst was filtered and the solvent was removed *in vacuo* yielding 1.04 g (100%) of gummy yellow crystals whose tlc showed one spot. Analytically pure **34** was secured by recrystallization from ethyl acetate: mp 135.5–136.5°; ir ($CHCl_3$) 3600–3380 (series of bands), 3160 (broad), 1663, 1610, 1545 (sh), 1525, 1505 (sh), and 1475 cm^{-1} (broad); uv 303 nm (ϵ 22,500); pmr δ 10.11 (broad s, 1 H), 6.60 (broad s, 2 H), 4.99 (s, 1 H), 4.67 (broad s, 1 H), 2.59 (s, 2 H), 1.95 (d, 2 H), 1.63 (s, 3 H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.23 (s, 3 H), 1.22 (s, 3 H); mass spectrum, calcd mol wt, 268.3; found, 268.5.

Anal. Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01. Found: C, 62.87; H, 9.26.

Semicorrins (4 and 35). Potassium metal (0.292 g, 7.5 mmol) was dissolved in 150 ml of hot reagent grade *tert*-butyl alcohol (preliminary drying of the alcohol inexplicably appears to have an adverse effect upon this reaction) and 1.0 g (3.7 mmol) of vinylogous carbinolamide **34** was added to the refluxing solution in 10 ml of *tert*-BuOH. An immediate color change from colorless to yellow was observed. This yellow solution was refluxed under N_2 for 12 hr, cooled, and neutralized to pH 7 with 10% HCl. The alcohol was removed under reduced pressure and the resultant yellow solid residue was dissolved in ether, washed with water, dried ($MgSO_4$), and concentrated yielding 0.85 g (90%) of relatively pure semicorrins **4** and **35**. Material of higher purity was obtained by vacuum sublimation (40° (0.1 mm)). Although tlc showed a single spot on silica gel the sublimed yellow-green crystals melted over a range of 73–85° suggesting a mixture of double bond isomers which was readily corroborated from the pmr spectrum: δ 5.53 (q, 0.8 H, J = 1.3 Hz), 5.21 (t, 1 H, J = 1.5 Hz), 5.10 (m, 0.4 H), 2.79 (d, 2 H, J = 1.5 Hz), 2.47 (t, 0.4 H, J = 2.0 Hz), 2.10 (d, 2.4 H, J = 1.3 Hz), 1.30 (s, 6 H), 1.17 (s, 6 H); ir ($CHCl_3$) 3200 (broad), 1723, 1642, 1620, and 1587 cm^{-1}; uv 262 (ϵ 5205) and 336 nm (ϵ 12,830). Satisfactory combustion data could not be obtained on this material due to its instability. However, mass spectrometric analysis of a freshly prepared sample further corroborated the assigned structure: mass spectrum m/e (rel intensity) 233 (13.7), 232 (75.0), 231 (8.8), 218 (15.0), 217 (100), 202 (11.3), and 189 (7.5).

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