Table I. Luminescence Data for *p*-Nitrobenzenes at 77°K

Molecule	Solvent	Fluorescence, nm	Phosphorescence, nm	τ_p, sec
Nitrobenzene	3MP, EtOH, MCH	None	None	
p-Dinitrobenzene	3MP, EtOH, MCH	None	None	
p-Nitrotoluene	3MP, EtOH, MCH	None	None	
p-Bromonitrobenzene	3MP, EtOH, MCH	None	None	
p-Nitrophenol	MCH	None	468, 500, ~530	0.15
	EtOH	None	500, 527, ~570	0.26
p-Nitroanisole	MCH, 3MP	None	481, 508, ~540	0.11
	EtOH	None	None	
p-Nitroaniline	MCH, 3MP	None	478, 507, ~540	
	EtOH	None	518, 542, ~580	0.40
p-Nitro-*N*,*N*-dimethylaniline	3MP, MCH	None	473, 505, 540, ~580	0.21
	EtOH	~460	530, 552, ~590	0.42

triplet species (D^* = 0.094 cm^{-1}) (Figure 9) appeared. The structure of this species is not known at present. No emission was observed on further photolysis.

Conclusion

Triplet nitrenes formed in the photolyses of *p*-diazidobenzene, phenyl azide, and 4,4′-diazidoazobenzene react at low temperature (77°K) in rigid glasses with dissolved oxygen to form diamagnetic and or paramagnetic species. These intermediates appear to rearrange to nitro compounds upon photolysis with uv or visible light. In the case of *p*-diazidobenzene for instance, this product, when photolyzed, leads to the formation of *p*-nitroazidobenzene. Further photolysis of this solution (or a fresh solution of *p*-nitroazidobenzene synthesized independently) leads eventually to the production of *p*-nitroaniline (in EtOH) or *N*-alkyl-*p*-nitroaniline (or in 3MP). The last two species are identified from their phosphorescence behavior. The luminescence behaviors of related nitrobenzenes studied during the course of this investigation are briefly discussed in Appendix I.

Appendix I

During the course of the preceding study we had occasion to investigate the luminescence of several simple substituted nitrobenzenes. Since there is relatively little data on these systems in the literature we thought it suitable to include these data in the present article. Figure 10 shows the luminescence obtained for *p*-nitroanisole and *p*-nitrophenol in alcohol or hydrocarbon solvents. The anisole did not appear to luminesce in alcohol. The results on all the materials studied are given in Table I.

Studies on the Synthesis of Corrins and Related Ligands. I. General Approach and Model Studies[1]

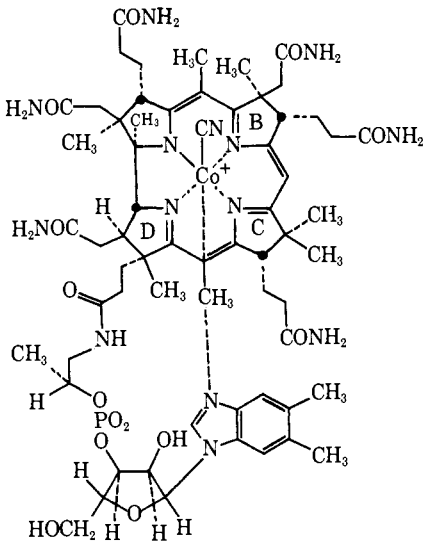
R. V. Stevens,*[2] C. G. Christensen,[3] William L. Edmonson,[3] Morris Kaplan, Edward B. Reid, and Mark P. Wentland[4]

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

Abstract: A fundamentally different approach to the synthesis of corrinoid substances is presented. The method involves the employment of isoxazole nuclei as a means of elaborating the crucial ring-bridging vinylogous amidine chromophores. Simple model systems were designed to test the feasibility of this approach. A simple synthesis of γ-substituted butyrolactams involving an unusually facile hydrolysis of β-cyano ketones and their conversion into semicorrinoid-like substances is outlined.

The detailed structure of vitamin B_{12} (**1**) was first revealed to the chemical world through the brilliant X-ray crystallographic studies of Crowfoot-Hodgkin.[5] In many respects this outstanding achievement may be regarded as a turning point in the history and development of the chemistry of natural products, since prior to this event, the discovery of the specific chemistry of new substances was secured most often as a by-product of extensive degradative studies. However, now, with an ever-increasing number of powerful physical tools at our disposal, we find ourselves in the rather enviable position of being able to ascertain even the most intimate structural details of a molecule often without ever having performed a single chemical transformation!

(1) For a preliminary account of a portion of this work, see R. V. Stevens and M. Kaplan, *Chem. Commun.*, 822 (1970).
(2) A. P. Sloan Fellow, 1969–1971.
(3) NSF Predoctoral Trainee.
(4) U. S. Public Health Service Predoctoral Fellow, 1967–1970.
(5) D. Crowfoot-Hodgkin, A. W. Johnson, and A. R. Todd, *Chem. Soc. Spec. Publ.*, **No. 3**, 109 (1955); D. Crowfoot-Hodgkin, J. Kamper, J. Lindsey, M. McKay, J. Pickworth, J. H. Robertson, C. B. Shoemaker, J. G. White, R. J. Prosen, and K. N. Trueblood, *Proc. Roy. Soc., Ser. A*, **242**, 288 (1957); for a review, see R. Bonnett, *Chem. Rev.*, **63**, 573 (1963).



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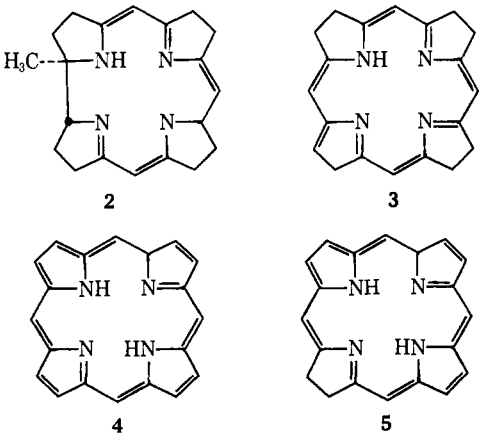
Although these exciting developments are to be applauded, they also create a void in our knowledge of the *chemistry* of new structural types. Regrettably, this is not a small price to pay. It is within this void that synthesis may be called upon to play an even more prominent role. In the present case this challenge has been accepted in a number of laboratories of which the enormous accomplishments of Eschenmoser,[6] Inhoffen,[7] Johnson,[8] and Woodward[9] are conspicuously noteworthy.

A New Approach to the Synthesis of Corrins

Of course, at the very heart of any synthetic project whose ultimate goal is vitamin B_{12} must be a concept for the elaboration of the central corrin framework, **2**. In consonance with this fact our initial task was reduced to the development of a reliable method for achieving this crucial goal. Should the plan we envisage prove worthy, then the application of this knowledge to the synthesis of the natural product itself can be considered seriously.

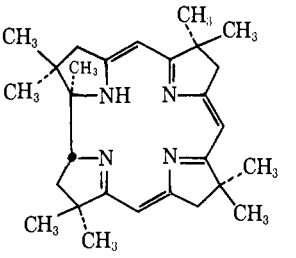
It is instructive to compare the various macrocyclic ligands incorporated by nature into some of its most important natural products.



2 3 4 5

It should cause no occasion for surprise that simple chlorins, **5**, are readily oxidized to porphyrins, **4**. In view of this fact the problems associated with preventing oxidation (or tautomerization) of an unsubstituted corrin, **2**, may be regarded as a virtual nightmare. Inspection of the vitamin B_{12} molecule reveals how nature defends itself against such oxidative and/or tautomeric disasters, *i.e.*, we note that the alternate peripheral carbons bear quaternary, hence nonenolizable, centers. However, even this substance is not entirely immune to oxidative and tautomeric transformations. For example, oxidative substitution reactions have, in fact, been observed at the unsubstituted β position of ring B.[10] Similar reactivity at the electronically equivalent positions of rings A and C are, as yet, unknown. This may possibly be attributed to a "shielding" influence of the adjacent *meso*-methyl functions whose absence, we should bear in mind, could alter substantially the reactivity of these centers. For these and other reasons the incorporation of vicinal quaternary centers at the corresponding positions of the basic corrin ligand **2** fully defines octamethylcorrin (**6**) as our initial synthetic target.

Having thus defined **6** as our goal, the central problem of any corrin synthesis comes into focus, and that is the question of how to elaborate the crucial ring-bridging vinylogous amidine systems. Of course, vinylogous



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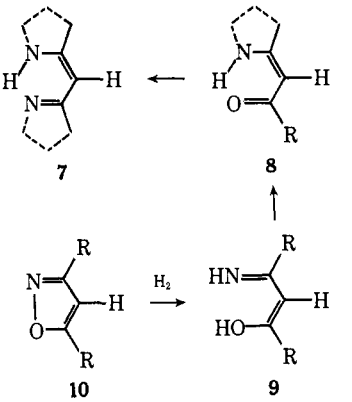
amidines, **7**, are simply aza analogs of vinylogous amides, **8**, which we regarded as attractive equivalent synthons. Among the various methods of synthesis of vinylogous amides which were considered, the catalytic hydrogenation of an appropriately substituted isoxazole, **10**, captured our imagination and, in fact, provided a suitable heuristic on which the strategy of our corrin synthesis is based.

One particular feature of this method of approach warrants additional comment. Although the mecha-



7 8 10 9

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

(7) H. H. Inhoffen, A. Gossauer, and D. Miehe, *Justus Liebigs Ann. Chem.*, **738**, 31 (1970), and previous papers.

(8) A. W. Johnson, *Chem. Brit.*, 253 (1967), and subsequent papers.

(9) See, for example, R. B. Woodward, *Pure Appl. Chem.*, 17, 519 (1968).

(10) R. Bonnett, J. R. Cannon, V. M. Clark, A. W. Johnson, L. F. J. Parker, E. L. Smith, and A. R. Todd, *J. Chem. Soc.*, 1158 (1957).

nistic details of isoxazole reduction remain obscure, **9** may be postulated as a reasonable intermediate in the ultimate production of the vinylogous amide. If we further assume that tautomerization of this intermediate proceeds *via* intramolecular proton transfer, then the required cisoid arrangement of the vinylogous amide **8** is virtually assured.

Simple Model Systems

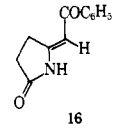
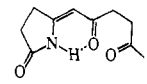
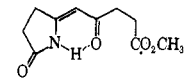
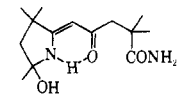
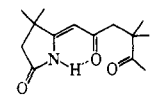
We, therefore, initiated a systematic investigation to explore the potential generality and/or limitations of employing isoxazoles as a scaffold for combining the essential elements of corrinoid substances. As will soon become apparent in the sequel, the substrates and products of this stage of our investigation were carefully selected to incorporate features which we felt would be useful in more precisely defining an actual corrin synthesis.

There are a number of ways known for the preparation of isoxazoles. However, only the rather well-defined cycloaddition of nitrile oxides and terminal acetylenes appeared suitable for our purposes. The nitrile oxides employed in this study have been generated *in situ* by one of the following three methods: phosphorus oxychloride or phenyl isocyanate induced dehydration of primary nitro compounds; lead tetraacetate catalyzed dehydrogenation of *syn*-aldoximes (*anti*-aldoximes fail to yield nitrile oxides with this reagent); and the reaction of either *syn*- or *anti*-aldoximes with *N*-bromosuccinimide in the presence of sodium methoxide or triethylamine.[11]

Thus, nitrile oxide (**12**) was generated *in situ* from nitro ester (**11**)[12] and allowed to react with phenylacetylene. *A priori* there were two possible orientations in which this cycloaddition could have occurred. Only that portrayed in **13** would be acceptable. Steric and electronic considerations led us to predict that the desired orientation should be favored and experiment impressively confirmed this prediction. None of the alternative isoxazole could be detected in the reaction mixture. In fact, we have as yet to detect significant amounts of this alternative mode of cycloaddition in any of the reactions we have attempted with terminal acetylenes, an observation in complete agreement with previous investigations[13] and of cardinal importance to our synthetic plans.

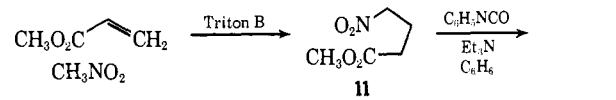
Isoxazole **13** was smoothly and quantitatively reduced with platinum catalyst in methanol solvent (the catalyst and solvent of choice inexplicably vary widely with the particular isoxazole being reduced[13]) and yielded exclusively the required cisoid vinylogous amide **14** or the cyclized material **15** but never a mixture of both. Quantitative cycloelimination of the elements of methanol from **14** was achieved simply by heating *in vacuo* (190° (0.2 mm)). A very small amount of the corresponding geometrical isomer **16** is also produced in this pyrolysis. The gross structural and stereochemical features of these and other intermediates reported herein were fully corroborated by their ir, pmr, and mass spectra and by combustion analysis (see the Experimental Section). In the present case assignment of the cisoid geometry to vinylogous amide **15** was established from its infrared spectrum which displayed intramolecular hydrogen bonding as confirmed by dilution studies. Furthermore, the position of the N–H stretching frequency for this substance conforms to the relative constant value observed throughout the entire series of such vinylogous amides which we have prepared (see Table I).

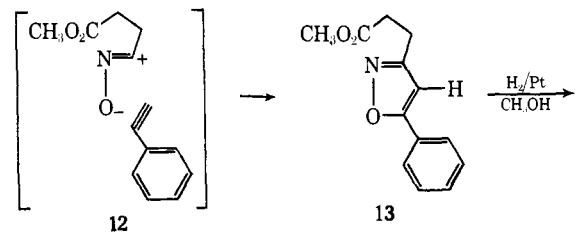
Table I

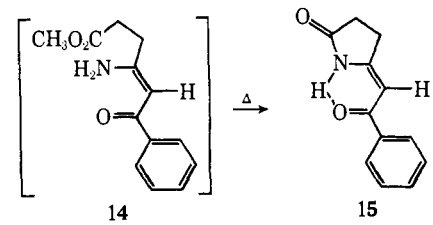
Compd	N–H ir absorption, cm^{-1}	Vinyl hydrogen pmr absorption (δ)
15	3300 ($CHCl_3$)	6.17
 **16**		6.50
	3300 ($CHCl_3$)[a]	5.60
	3290 (KBr)[a] 3330 ($CHCl_3$)	5.52
21	3295 ($CHCl_3$)	5.80
	*Ca.* 3295 ($CHCl_3$)[a]	4.98
	3300 ($CHCl_3$)[a]	5.32

[a] See ref 16.

Triton B







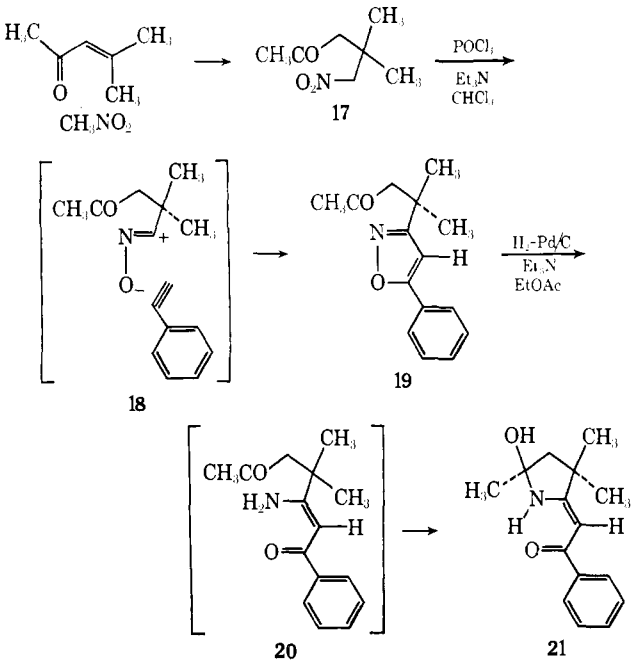
The substantially more hindered tertiary nitrile oxide (**18**) was generated *in situ* by phosphorous oxychloride

(11) *Cf. inter alia*, C. Grundmann, *Synthesis*, 344 (1970); N. K. Kochetkov and S. D. Sokolov, *Advan. Heterocycl. Chem.*, **2**, 365 (1963).

(12) J. Colonge and J. M. Pouchol, *Bull. Soc. Chim. Fr.*, 596 (1962).

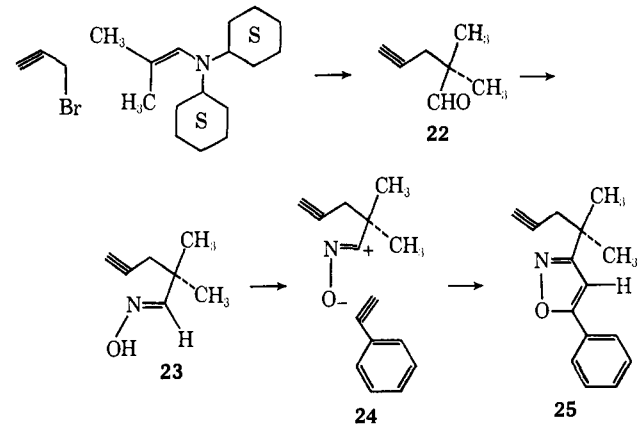
(13) For previous reductions of this type see: G. Shaw and G. Sugowdz, *J. Chem. Soc.*, 665 (1954); P. Braro, G. Gaudiano, A. Quilico, and A. Ricca, *Gazz. Chim. Ital.*, **91**, 47 (1961); G. Stagno d'Alcontres, *ibid.*, **80**, 441 (1950); P. Pino, F. Piacenti, and G. Fatti, *ibid.*, **90**, 356 (1960); D. N. McGregor, U. Corbin, J. E. Swigor, and L. C. Cheney, *Tetrahedron*, **25**, 389 (1969); G. Casnati, A. Quilico, A. Ricca, and P. Vita Finzi, *Tetrahedron Lett.*, 233 (1966); H. Kano and Y. Makisumi, *Pharm. Bull.*, **3**, 270 (1955); G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967), and subsequent papers.

induced triethylamine-catalyzed dehydration of the corresponding nitro ketone **17**[14] in the presence of phenylacetylene. Once again only the 3,5-disubstituted isoxazole **19** was detected in the reaction mixture.[15] Reduction of this substance was best achieved by means of a palladium/charcoal catalyst in the presence of triethylamine. The resultant vinylogous amide **20** spontaneously cyclized to the corresponding carbinolamide **21**. Once again only the cisoid geometry was observed.

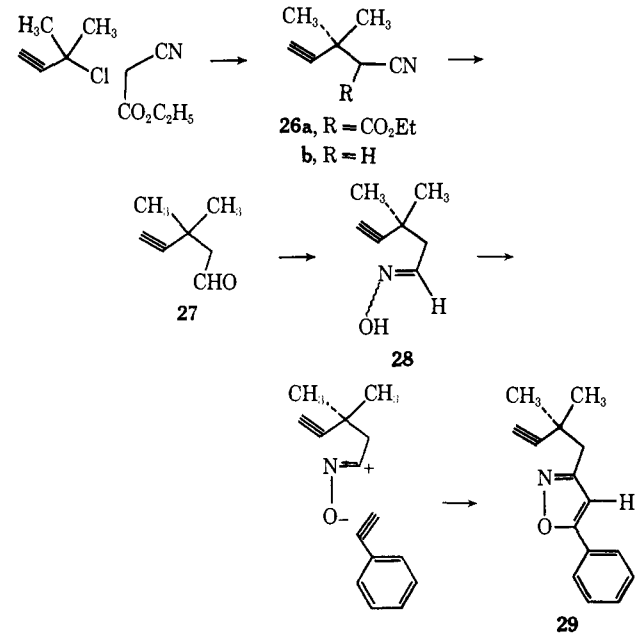


The question naturally arose that if one isoxazole could be employed as an equivalent synthon for one of the crucial ring-bridging vinylogous amidine chromophores, then quite possibly by the judicious incorporation of more than one such isoxazole into the same molecule an expeditious synthesis of a network of such systems could be achieved. This intriguing possibility would obviously require some means of joining preexisting isoxazole nuclei. The incorporation of either a terminal acetylene function or a suitable nitrile oxide precursor on one of the isoxazole side chains appeared to be one obvious way of achieving this result. With this in mind two other simple model systems have been investigated. As will become apparent in the sequel[16] the particular nitrile oxides employed in this model study were selected for their potential further deployment in actual corrin synthesis.

Nitrile oxide **24** was conveniently generated by low-temperature lead tetraacetate oxidation of the tertiary aldoxime **23** (which exists exclusively in the required syn configuration). Inter- or less likely intramolecular self-condensation of this dipolarophile was satisfactorily suppressed by employment of a generous (fivefold) excess of phenylacetylene. The desired isoxazole, **25**,



was secured in 60% yield without extensive further investigation of the reaction conditions. By contrast, pmr analysis[17] of the primary aldoxime **28**, prepared in the manner indicated below (see the Experimental Section), revealed that it consisted of an inseparable mixture[18] of approximately 60% syn:40% anti geometrical isomers. Since it had been previously established[19] that only the syn isomer is capable of yielding a nitrile oxide, we were not surprised to discover that attempts to prepare isoxazole **29** by this method proceeded in very low yield. By contrast, bromination of the sodium salts of the mixture of isomeric aldoximes with *N*-bromosuccinimide in neat phenylacetylene was relatively more satisfactory demonstrating the expected independence of oxime geometry on the course of this reaction.[20]



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

(15) Little effort was extended during this stage of the investigation to maximize yields since, in general, they were more than satisfactory for the purposes intended. Later in our work (when yields *had* to be improved) we have been able to adjust reaction conditions to achieve satisfactory results.

(16) See Part II: R. V. Stevens, L. E. DuPree, Jr., W. L. Edmonson, L. L. Magid, and M. P. Wentland, *J. Amer. Chem. Soc.*, **93**, 6637 (1971).

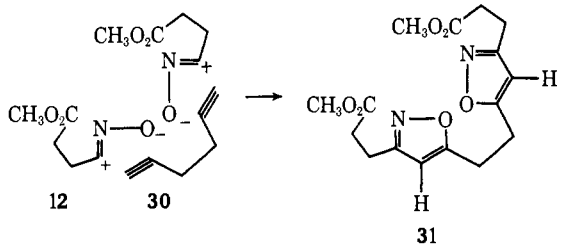
(17) I. Pejkovic-Tadic, M. Hranisavljevic-Jakovljevic, S. Nesic, C. Pascual, and W. Simon, *Helv. Chim. Acta*, 48, 1157 (1965); W. D. Phillips, *Ann. N. Y. Acad. Sci.*, 70, 817 (1958); E. Lusting, *J. Phys. Chem.*, 65, 491 (1961).

(18) The separation, by chromatographic techniques, of such mixtures of syn and anti oximes of aliphatic C_2–C_{10} aldehydes is possible, but it is also known that they readily revert to an equilibrium mixture of both geometrical isomers: see I. Pejkovic-Tadic, M. Hranisavljevic-Jakovljevic, and S. Nesic, *J. Chromatogr.*, 21, 239 (1966).

(19) G. Just and K. Dahl, *Tetrahedron*, 24, 5251 (1968).

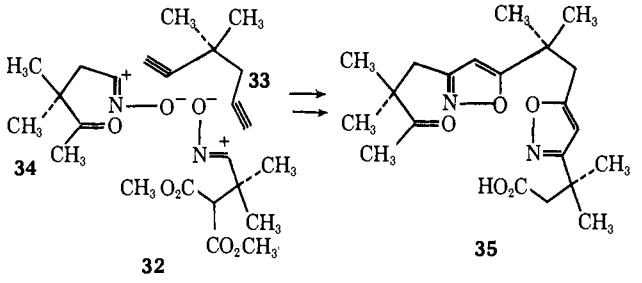
(20) This procedure involved a slight modification of the method used for preparing stable nitrile oxides recently introduced by Grundmann.[11] The reaction presumably proceeds through an α-bromonitroso intermediate. Subsequent deprotonation and loss of bromide ion has ample analogy to the rather well-known 1,3 elimination of the elements of HX from hydroxamic halides.[11]

An alternative method for incorporating more than one isoxazole nucleus into the same molecule was also investigated. In this case 2 equiv of the familiar nitrile oxide **12** was allowed to react with the simple diacetylene **30** from which the highly crystalline bisisoxazole **31** was easily secured.



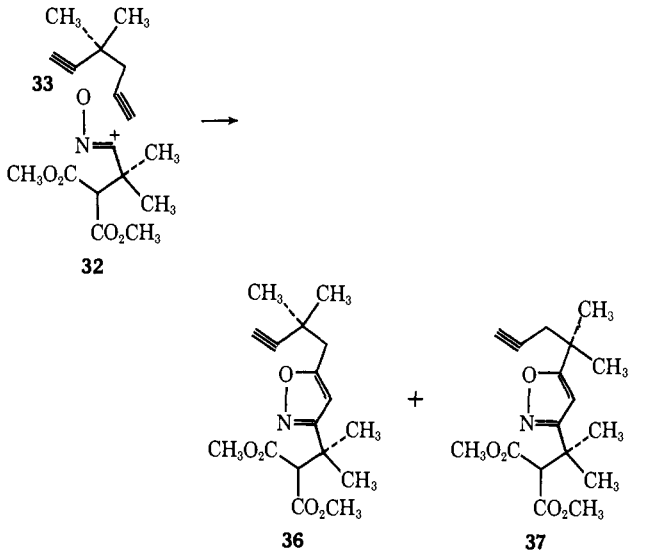
12 **30** **31**

We were naturally encouraged by this result. However, to be of any real value in actual corrinoid synthesis it would be necessary to employ two different nitrile oxides and an unsymmetrical diacetylene in a carefully defined sequence. Thus, we reasoned that if the hindered tertiary dipolarophile **32**[16] reacted selectively with the apparently less-hindered triple bond of the unsymmetrical diacetylene **33**,[21] then subsequent cycloaddition of the relatively unhindered primary nitrile oxide **34** to the resultant monoisoxazole should yield bisisoxazole **35**. The latter substance could be considered as an equivalent synthon for three of the four required vinylogous amidine systems complete with a proper geminate disubstitution pattern.



34 **33** **32** **35**

Therefore, we were disappointed and somewhat surprised to observe that the initial cycloaddition of **32** and **33** was not in the least bit selective. A 1:1 mixture of both possible monoisoxazoles, **36** and **37**, was secured from the reaction mixture. Even more annoying was the fact that we could not effect their separation.



33 **32** **36** **37**

We have also uncovered a fundamentally different approach to the synthesis of simple semicorrinoid substances. Lapworth had reported in 1904[22] that the conjugate addition of excess cyanide in warm aqueous alcohol to mesityl oxide yields the cyanohydrin (mp 165–166°) of the expected cyano ketone **38**. The structural assignment was made on the basis of its nitrogen analysis and solubility in cold aqueous base and the fact that a hot alkaline solution liberated HCN. We have repeated this experiment and have isolated two crystalline substances in variable yield depending upon the exact conditions employed. One of these melted at 168–169° and behaved like Lapworth's cyanohydrin. However, the spectral features of this substance were clearly inconsistent with the assigned structure. We now reformulate this compound as the γ-cyanobutyrolactam (**40**) on the basis of its spectral properties and carbon–hydrogen–nitrogen analysis which agreed with the assigned structure (note **40** and the cyanohydrin of **38** have the same empirical formula). The other crystalline compound was the known[23] carbinolamide **39** and its isolation from the same reaction mixture clarified the origin of **40** and provided the means for its rational synthesis.

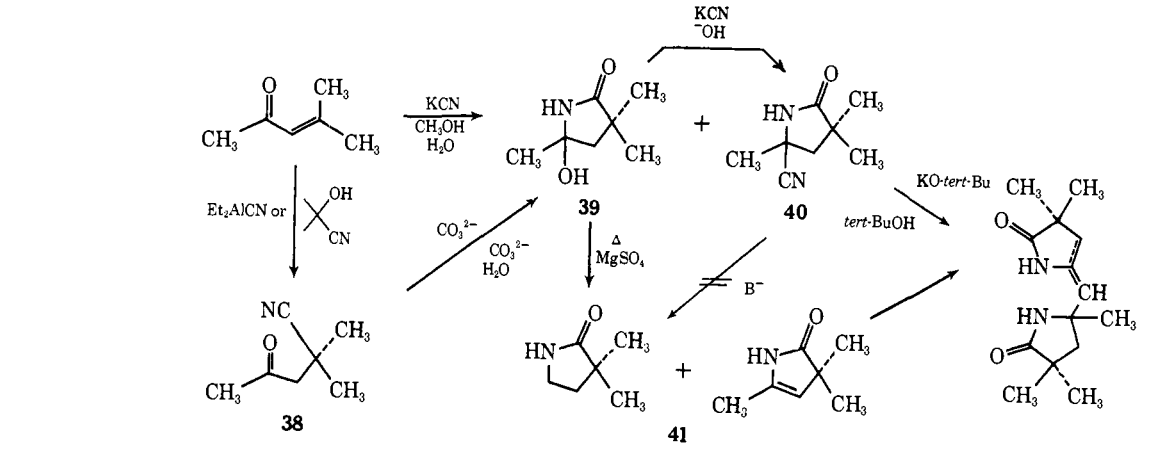
Although the mechanistic details of these remarkable transformations remained somewhat uncertain, the results were of sufficient interest to corrin synthesis to warrant a more extensive investigation. The initial conjugate addition step is, of course, well known to be accompanied by the generation of base in the aqueous medium employed in this reaction. Subsequent hydrolysis of the cyano function can, therefore, be rationalized. However, the apparent ease and efficiency with which this is accomplished led us to postulate that the neighboring carbonyl function was involved in this process in the manner portrayed below. The observed carbinolamide **39** is, therefore, simply the result of an expected ring-chain tautomerization. Base-induced dehydration of **39** and trapping of the resultant intermediate, **42**, by nucleophilic cyanide ion provides a plausible explanation of the origin of **40** in the reaction mixture. This was easily confirmed independently by exposing **39** to a basic cyanide solution which provided **40** in high yield. Confirmation of the postulated neighboring group participation sequence is more difficult to unambiguously establish. However, the additional observation that simply warming an aqueous alcoholic solution of **38** (prepared from mesityl oxide and "Et_2AlCN" or acetone cyanohydrin) in pH 10 Na_2CO_3–$NaHCO_3$ buffer also afforded **39** in 84% yield was of special interest. This unusually mild hydrolysis is without precedence with simple aliphatic nitriles, and strongly implicates the involvement of the carbonyl function as we had postulated.

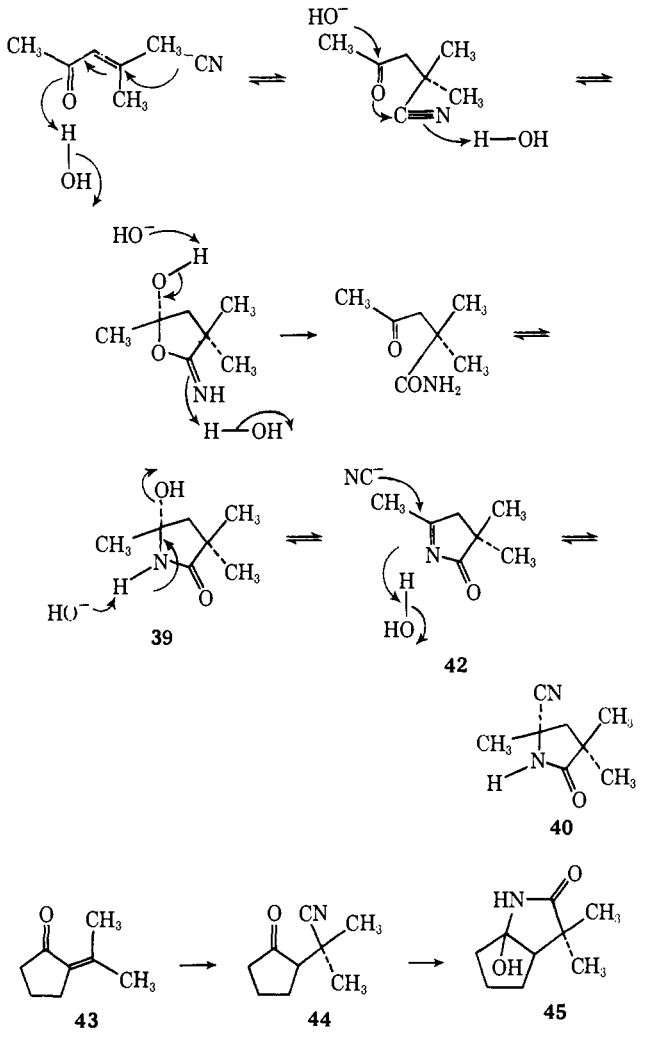
A further test of the facile hydrolysis step involved cyano ketone **44**. By warming this substance in the same pH 10 buffer employed above, the corresponding carbinolamide **45** could be secured in 60% yield.

(21) The synthesis of this substance is described in the Experimental Section of this paper.

(22) A. Lapworth, *J. Chem. Soc.*, 1214 (1904).

(23) A. Haller and E. Bauer, *C. R. Acad. Sci.*, 158, 1086 (1914).





With a practically unlimited supply of intermediate **40** available, it became of interest in connection with corrin synthesis to see if base-induced elimination of HCN might be followed by deprotonation to the exocyclic position as shown below. Provided the base was a hindered one, such a proposition appeared sterically and electronically favorable. Furthermore, such an anion could then serve as a nucleophile toward its own precursor in much the same manner as cyanide had in the **42** to **40** transformation. In principle, it appeared likely that these same considerations could be applied to the mixture of tautomeric enamides, **41**, prepared in quantitative yield by the pyrolytic dehydration of carbinolamide **39** in the presence of $MgSO_4$. Indeed, when **40** (or the isomeric mixture **41**) was exposed to slightly more than 1 equiv of KO-*tert*-Bu in warm *tert*-BuOH a mixture of two crystalline dimeric substances was obtained. The dimeric nature of these two materials was established from combustion, and mass spectral data. Except for the rather delicate question of the geometry of its double bond, one of the dimers could be assigned structure **46** on the basis of its ir and pmr spectra. The exocyclic enamide chromophore, λ_{max} 232 nm (ϵ 11,600) compares favorably with that found in the related known[6] dimeric compound **47**, *i.e.*, 229 nm (12,900). The structure of the other crystalline dimer, mp 183–184°, remains less certain although the spectral evidence is suggestive of the corresponding endocyclic double bond isomer **48**. Catalytic hydrogenation of each of the dimeric compounds provided the same two stereoisomeric reduction products, confirming the isomeric nature of these compounds.

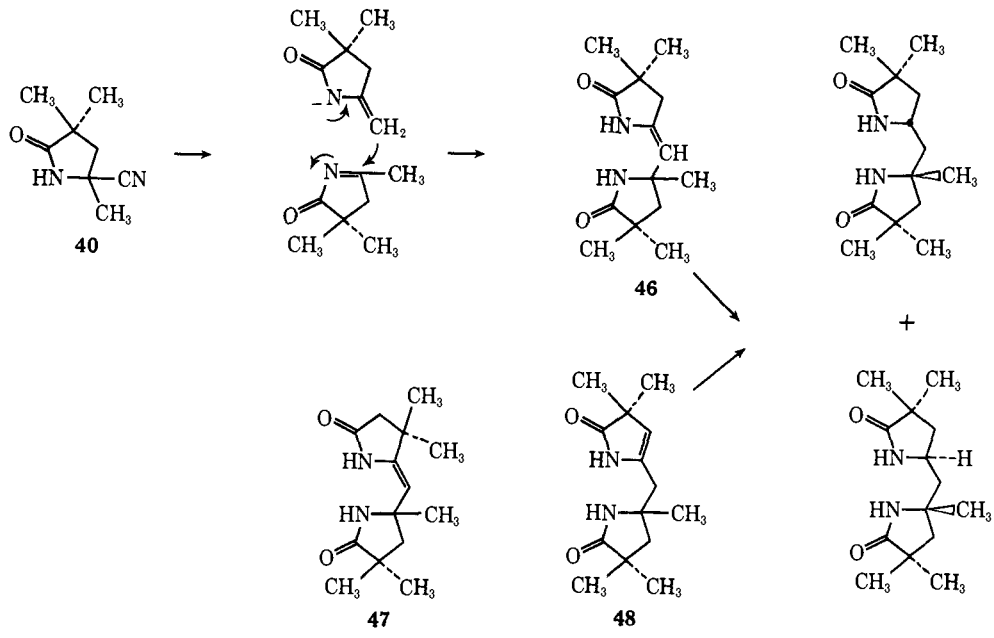
Experimental Section[24]

3-(2-Carbomethoxyethyl)-5-phenylisoxazole (13). A mixture of 0.74 g (5 mmol) of 4-nitromethyl butanoate (**11**),[12] 0.77 g (7.5 mmol) of freshly distilled phenylacetylene, 1.5 ml (14 mmol) of phenyl isocyanate, and 50 ml of dry benzene was combined and several drops of freshly distilled (from $LiAlH_4$) triethylamine were added. The mixture was allowed to stir for 3 days. The precipitated diphenylurea was removed by filtration and the filtrate was freed from solvent and chromatographed on a silica gel column. Elution with benzene yielded the desired isoxazole which was recrystallized from either cyclohexane or petroleum ether and afforded 0.35 g (30%) of white needles: mp 93.5–94.5°; ir ($CHCl_3$) 1722 and 1611 (m) cm^{-1}; uv max 262.5 nm (ϵ 1.63 × 10^4); pmr δ 7.90–7.40 (m, 5 H), 6.43 (s, 1 H), 3.76 (s, 3 H), and 3.25–2.62 (m, 4 H); mass spectrum, calcd mol wt, 231.3; found, 231.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67. Found: C, 67.46; H, 5.72.

Vinlogous Amides 14 and 15. The isoxazole **13** was reduced in methanol solvent over PtO_2 (Adams Catalyst) at atmospheric pressure and room temperature. After the reduction was complete the catalyst was removed by filtration and the solvent was removed *in vacuo*. Reduction was quantitative and only one product had ever been observed in all experiments. Inexplicably, that one product was either the open-chain vinylogous amide **14**

(24) Infrared spectra were obtained on a Beckman IR-8 spectrophotometer; ultraviolet spectra are of 95% ethanol solutions and were recorded on Cary Model 14 or Bausch and Lomb Spectronic 505 spectrometers. 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.



or its cyclized partner **15** and never a mixture of both. The cyclized product **15** is a white solid and in those instances when it was obtained directly from the reduction it was simply recrystallized from CCl_4: mp 133–135°; ir ($CHCl_3$) 1748, 1642, 1588, and 1562 cm^{-1}; uv max 257.5 (ϵ 11,500) and 307.5 nm (ϵ 35,900); pmr δ N–H very broad *ca.* 11.3–10 (1 H), 8.00–7.35 (m, 5 H), 6.17 (t, 1 H), 3.17–2.33 (m, 4 H); mass spectrum, calcd mol wt, 201.2; found, 201.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51. Found: C, 71.60; H, 5.79.

The uncyclized product **14** is a yellow-green oil: ir (neat) 1730, 1610, 1570, and 1525 cm^{-1}; pmr δ 8.00–7.30 (m, 5 H), 5.73 (s, 1 H), 3.70 (s, 3 H), 2.60 (t, 4 H). Ring closure to **15** occurs very slowly at room temperature but more rapidly upon heating. A "Kugelrohr" apparatus (Rinco Instrument Co., Inc.) is placed in a vertical position and **14** heated at 190° *in vacuo* (0.2 mm) until solidification in the cool chamber is complete. The solid **15** obtained in this way is contaminated with a small amount of the geometrical isomer **16** which can be removed by careful sublimation (80° (0.1–0.3 mm)). The "undesired" isomer was not extensively purified but had a mp of ~118°.

3-(1,1-Dimethyl-3-oxobutyl)-5-phenylisoxazole (19). A mixture of 6.39 g (0.04 mol) of 5-nitro-4,4-dimethyl-2-pentanone (**17**),[14] 4.02 g (0.04 mol) of phenylacetylene, 18.14 g (0.18 mol) of Et_3N (freshly distilled from CaH), and 200 ml of dry $CHCl_3$ was charged into a 500-ml flask and cooled to 0°. $POCl_3$ (0.7 g, 0.044 mol) was then added dropwise, under N_2, over a 5-min period and the evolution of HCl was noted. Stirring was continued at 0° for 1 hr and then the solution was refluxed for 2 hr. The resultant dark solution was washed with H_2O and then dilute Na_2CO_3, dried over $MgSO_4$, and finally freed of solvent. Distillation yielded 1.5 g (15%) of crude isoxazole **19** (*ca.* 154° (0.21 mm)). The distillate solidified upon standing and an analytically pure sample was secured by recrystallization from cyclohexane: mp 79.5°; ir (KBr) 3125, 1712, 1612, 1594, and 1574 cm^{-1}; pmr δ 7.59 (m, 5 H), 6.49 (s, 1 H), 2.90 (s, 2 H), 2.09 (s, 3 H), 1.49 (s, 6 H); mass spectrum, calcd mol wt, 243.30; found, 243.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.05; N, 5.76. Found: C, 74.07; H, 7.17; N, 5.54.

Vinylogous Carbinolamide (21). A solution of 1.10 g (4.5 mmol), of isoxazole **19** in 100 ml of EtOAc and 100 ml of Et_3N (freshly distilled from CaH) was cautiously added to 30 mg of 10% Pd/C in a 500-ml Parr bomb and reduced at 40.5 psi. The catalyst was filtered and the solution was concentrated *in vacuo* yielding a pale yellow solid whose tlc (benzene–ether, 3:1) revealed a single new spot and starting material. A portion of this crude mixture was purified by preparative layer chromatography (same solvent system): ir ($CHCl_3$) 3605, 3380, 1603, and 1580 cm^{-1}; pmr δ 8.20–7.60 (m, 5 H), 5.80 (s, 1 H), 3.28 (s, 1 H), 2.03 (AB q, 2 H), 1.63 (s, 3 H), 1.47 (s, 3 H), 1.30 (s, 3 H).

2,2-Dimethyl-4-pentynal (22). The dicyclohexylenamine of isobutyraldehyde[25] (160 g), propargyl bromide (85 g), and CH_3CN (210 ml) was stirred for 72 hr under N_2 at 45° after which the solvent was removed *in vacuo* and the oily residue was poured into 950 ml of 10% KOH and stirred vigorously for 2 hr. The organic layer was extracted into ether, washed with saturated NaCl, and dried over Na_2SO_4. The ether was evaporated and the product was distilled to give 50.6 g (68%) of the desired aldehyde:[25] bp 138–140°; pmr (CCl_4) δ 1.13 (s, 6 H), 1.97 (t with further fine splitting, 1 H), 2.28 (d, 2 H), 9.48 (s, 1 H); ir (neat) 3300, 2105, and 1719 cm^{-1}.

Syn Oxime of 22. Aldehyde **22** (5 g), $NH_2OH \cdot HCl$ (3.26 g), and pyridine (8 ml) were mixed. The reaction mixture became quite warm and was stirred for 1 hr at room temperature and then an additional hour at 55° and then dissolved in CH_2Cl_2 and washed with H_2O (three 100-ml portions). The aqueous layer was extracted with CH_3Cl_2 and the combined fractions were dried over Na_2SO_4 and freed of solvent. Distillation gave 5.07 g (90%) of pure *syn*-aldoxime (**23**): bp 92° (17 mm); pmr (CCl_4) δ 1.18 (s, 6 H), 1.96 (t with further fine splitting, 1 H), 2.25 (d, 2 H), 7.22 (s, 1 H), 8.90 (broad s, 1 H); ir (neat) 3620–3000 (s), 3310 (s), 1640 (vw), 1367 and 1385 cm^{-1} (m); mass spectrum, calcd mol wt 125.09; found 125.

3-(1,1-Dimethyl-3-butyne)-5-phenylisoxazole (25).[19] To a well-stirred solution of aldoxime **23** (0.5 g) and phenylacetylene (4.8 g) in CH_2Cl_2 maintained at −78° was added all at once a cold (−78°) solution of $Pb(OAc)_4$ (2.13 g) in 18 ml of CH_2Cl_2 and the mixture was stirred for 2 hr at −78°. A cold (−78°) solution of Et_3N (1.12 g) in 9 ml of CH_2Cl_2 was then added and the mixture was allowed to warm to room temperature and stirred for 2 days. $MgSO_4$ (1.5 g) and 50 ml of Et_2O were added and the suspension was stirred an additional hour. After filtration the organic layer was washed with cold saturated $NaHCO_3$ (five 10-ml portions) and dried over Na_2SO_4. The Et_2O and CH_2Cl_2 were evaporated and the excess phenylacetylene was removed by distillation (17 mm). The dark residue solidified upon cooling and was sublimed at 70° (0.1 mm) and finally recrystallized from MeOH providing 0.55 g (61%) of isoxazole **25**: mp 85.5–86°; pmr δ 1.47 (s, 6 H), 2.02 (t with further fine splitting, 1 H), 2.58 (d, 2 H), 6.48 (s, 1 H), 7.33–7.88 (m, 5 H); ir (KBr) 3270 (s), 1611, 1590, 1571, 760 cm^{-1}; mass spectrum, calcd mol wt, 225.29; found, 225.

Ethyl 2-Cyano-3,3-dimethyl-4-pentynoate (26a). To a 1-l. three-necked flask fitted with a reflux condenser, N_2 inlet, and drying tube, 500 ml of EtOH and 6.94 g (1 mol) of Li wire were added. The mixture was stirred magnetically with cooling as necessary until all the Li had reacted. Ethyl cyanoacetate (113 g, 1 mol) was added and the cloudy mixture was stirred until it became clear, and then 51.75 g (0.5 mol) of 3-chloro-3-methyl-1-butyne was added to the solution at room temperature and the mixture was stirred for 2 days. The solution was concentrated to about half its original volume, 150 ml of ether was added, and it was cooled to about −10°

(25) G. Opitz and H. Mildenberger, *Justus Liebigs Ann. Chem.*, **650**, 122 (1961).

and washed with 150 ml of cold 4 *N* HCl, two 50-ml portions of H_2O, five 50-ml portions of saturated $NaHCO_3$, and two 50-ml portions of saturated NaCl. The acidic wash was reextracted with ether and the ether extract was neutralized as above. The combined ether extracts were dried over K_2CO_3 and then freed of solvent. The residue was then distilled through a 30-cm jacketed Vigreux column providing 38.4 g (43%) of pure **26a**: bp 67–69° (0.2 mm); ir (neat) 3295, 2250, 2120, 1750, 1394, and 1370 cm^{-1}; pmr δ 4.30 (q, 2 H, J = 7 Hz), 3.62 (s, 1 H), 2.42 (s, 1 H), 1.48 (s, 6 H), 1.32 (t, 3 H, J = 7 Hz). Further proof of structure is provided by subsequent conversion to **26b** and **27**.

3,3-Dimethyl-4-pentynonitrile (26b). A 250-ml flask was equipped with reflux condenser, thermometer, and N_2 inlet and charged with 75 ml of ethylene glycol and 11.5 g (0.205 mol) of KOH pellets. The KOH was dissolved by warming and 18.9 g (0.1 mol) of cyano ester **26a** was added to the solution which was then immersed in an oil bath preheated to *ca.* 140°. The solution was refluxed for 0.5 hr (~120° inner temperature), allowed to cool to room temperature, and poured into 150 ml of ice water. The aqueous solution was extracted with ether (three 75-ml portions) and the combined ether extracts were washed with three 30-ml portions of H_2O and two 30-ml portions of saturated NaCl, and dried over $MgSO_4$. The ether was carefully removed under reduced pressure, and the residue was distilled at atmospheric pressure to yield 7 g (65%) of pure **26b**: bp 160–161°; ir (neat) 3300, 2250, 1370, 1390, and 2110 cm^{-1}; pmr δ 2.50 (s, 2 H), 2.25 (s, 1 H), 1.35 (s, 6 H); mass spectrum, calcd mol wt, 107.2; found, 107.

3,3-Dimethyl-4-pentynal (27). The reaction was conducted under a N_2 atmosphere in a 50-ml two-necked flask equipped with magnetic stirrer, addition funnel, and reflux condenser. To 1.5 g (14 mmol) of nitrile **26b** dissolved in 15 ml of dry benzene was added 8 ml of a solution of diisobutylaluminum hydride (Texas Alkyls Inc.) in benzene (concentration, 0.28 g/ml, 15.8 mmol). A mildly exothermic reaction resulted as the hydride solution was slowly added. After the addition was complete the solution was heated to 45–50° for 4 hr and then cooled; aqueous HCl was added cautiously to the vigorously stirred solution. An induction period was observed during the acid addition before a vigorous reaction ensued, liberating a great deal of gas forming a thick gel which impedes efficient stirring. Enough acid was added to dissolve the aluminum salts; ether was then added and the layers were separated. The aqueous layer was further extracted with ether and the organic extracts were combined, dried over $MgSO_4$, and then distilled at atmospheric pressure to give 0.65 g (42%) of aldehyde **27**: bp 132–134°; ir (neat) 3295 and 1725 cm^{-1}; pmr δ 9.62 (t, 1 H, J = 2.5 Hz), 2.31 (d, 2 H, J = 2.5 Hz), 2.13 (s, 1 H), 1.30 (s, 6 H).

The aldehyde forms a crystalline 2,4-DNP: mp 100–101° (95% EtOH); mass spectrum, calcd mol wt, 290.3; found, 290.

Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86. Found: C, 53.78; H, 5.18.

Oxime of 3,3-Dimethyl-4-pentynal (28). The same procedure as described for **23** was employed: bp 120–122° (42 mm); ir (neat) 3300 cm^{-1}; pmr δ 9.37 (broad s, 1 H), 7.45 (t, 1 H, J = 6.5 Hz, syn isomer, 60%), 6.85 (t, 1 H, J = 5.5 Hz, anti isomer, 40%), 2.47 (d, 2 H, J = 5.5 Hz), 2.27 (c, 2 H), J = 6.5 Hz), 2.10 (s, 1 H), 1.27–1.23 (pair of closely spaced singlets, 6 H).

3-(2,2-Dimethyl-3-butyne)-5-phenylisoxazole (29). The isomeric aldoxime (**28**) (166 mg, 1.33 mmol) was dissolved in 2 ml of dry ether and the system was purged with N_2 and cooled to −70° in a Dry Ice–acetone bath, and 0.92 ml (1.33 mmol of *ca.* 1.45 *N*) of *n*-butyllithium in pentane solution was added with stirring over about 5 min. The suspension was allowed to warm to room temperature and stirred for 0.5 hr; then 3 ml (2.8 g, 27 mmol) of phenylacetylene was added to the salt suspension and 235 mg (1.35 mmol) of *N*-bromocuccinimide was added in several portions over 0.5 hr. The yellow heterogeneous mixture was stirred under N_2 in the dark for 12 hr, then poured into 10 ml of 1 *N* NaOH, and extracted with three 10-ml portions of $CHCl_3$. The organic phases were combined, washed with three 10-ml portions of H_2O, and dried ($MgSO_4$), and the solvent and excess phenylacetylene were removed first on a rotary evaporator, then *in vacuo*. This yielded 141 mg of a mixture containing about 75% (pmr analysis) of **29** corresponding to a 35% yield. Acidification and extraction of the basic aqueous phases yielded 76 mg (46%) of recovered oxime (**28**). The crude product was purified by column chromatography on silica gel. Removal of solvent *in vacuo* provided pure **29** as colorless crystals: mp 61–61.5°; ir 3315, 2120, 1595, 1375, 1387, and 760 cm^{-1}; pmr δ 7.30–7.85 (m, 5 H), 6.61 (s, 1 H), 2.85 (s, 2 H), 2.20 (s, 1 H), 1.30 (s, 6 H); mass spectrum, calcd mol wt, 225.28; found 225.

Bisisoxazole Diester (31). To a solution of 2.96 g of 1,5-hexadiyne[26] (**30**) and 3 ml of Et_3N (freshly distilled from $LiAlH_4$) in 500 ml of benzene were added 11.02 g of 11 and 20.1 g of phenyl isocyanate at room temperature with stirring under N_2. The mixture became cloudy after about 0.5 hr as the diphenylurea precipitated. Stirring was continued for 4 days and then the mixture was cooled and filtered. Concentration of the filtrate under reduced pressure precipitated more diphenylurea which was triturated with several portions of $CHCl_3$. The solvent was removed once again, then redissolved in $CHCl_3$ and filtered. Upon evaporation 4.63 g (35%) of solid bisisoxazole **31** was obtained which was recrystallized from benzene: mp 118–119°; pmr δ 2.57–3.12 (m, 4 H), 3.14 (s, 4 H), 3.73 (s, 6 H), 5.91 (s, 2 H); ir 1727 and 1600 cm^{-1}; mass spectrum, calcd mol wt, 336.35; found, 336.

Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.99. Found: C, 57.26; H, 6.15.

3,3-Dimethyl-1,5-hexadiene. Magnesium (14.58 g) and Hg (46 ml) were placed in a flame-dried flask and stirred for 3 hr. The amalgam was covered with a layer of Et_2O and a solution of methylene iodide (83.55 g) and 2,2-dimethyl-4-pentenal[27] (33.66 g) in 120 ml of Et_2O was added dropwise. The mixture was refluxed for 0.5 hr, saturated aqueous NH_4Cl was added, and it was steam distilled. The distillate was saturated with NaCl, extracted with Et_2O (two 75-ml portions), dried over Na_2SO_4, and fractionally distilled to give 18.6 g (56%) of the diene:[28] bp 100–101°; pmr neat δ 1.00 (s, 6 H), 2.03 (d, with further fine splitting, 2 H), 4.70–5.17 (m, 4 H), 5.42–6.15 (m, 2 H); ir (neat) 1640, 1363, 1378, and 910 cm^{-1}.

3,3-Dimethyl-1,5-hexadiyne (33) was prepared by bromination of the above diene followed by dehydrobromination with $NaNH_2$ in NH_3[26] in 50% overall yield: bp 103–104°; pmr δ 1.31 (s, 6 H), 2.05 (t, with further fine splitting, 1 H), 2.12 (s, 1 H), 2.38 (d, 2 H); ir (CCl_4) 3312, 2112, 1367, and 1387 cm^{-1}; mass spectrum, calcd mol wt, 106.17; found 106.

4-Cyano-4-methyl-2-pentanone (38). The procedure was essentially that of Nagata.[29] To a solution of Et_3Al in toluene (136 g of a 25% solution, 0.28 mol) which was stirred and cooled in an ice bath was added a solution of 10 g of HCN in 35 ml of benzene. After evolution of ethane ceased a solution of 25 g (0.25 mol) of mesityl oxide in 10 ml of benzene was added dropwise to the cooled solution and stirring was continued for 1 hr. After a further 2 hr, the solution was poured in portions into 200 ml of 10% KOH cooled with crushed ice. The mixture was extracted with $CHCl_3$, dried ($MgSO_4$), and freed of solvent. Distillation gave 17.2 g (55%) of a colorless oil: bp 52–53° (0.15 mm), lit.[30] bp 82° (4 mm).

5-Hydroxy-3,3,5-trimethylbutyrolactam (39). A solution of cyano ketone **38** (17.2 g) in 40 ml of $NaHCO_3$–Na_2CO_3 pH 10 buffer and 10 ml of EtOH was refluxed gently for 26 hr. The solution was cooled and the product, which precipitated on scratching, was filtered off and washed with a little water. The volume of the filtrate was reduced yielding a second crop; total yield was 14.6 g (84%). The carbinolamide was recrystallized from EtOH–H_2O as tiny colorless crystals: mp 152.5–153.5°; ir (Nujol) 3400, 3220, and 1670 cm^{-1}; pmr δ 1.98 (s, 2 H), 1.43, 1.19, 1.07 (all singlets, 3 H each); mass spectrum, calcd mol wt, 143.18; found, 143.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.8; H, 9.1; N, 9.8. Found: C, 58.9; H, 9.1; N, 9.9.

5-Cyano-3,3,5-trimethylbutyrolactam (40). To a solution of KCN (60 g, 0.92 mol) in 200 ml of water and 400 ml of CH_3OH stirred vigorously at 50–60° (bath temperature) was added a solution of mesityl oxide (39 g, 0.4 mol) in 45 ml of CH_3OH over a period of 2.5 hr. Stirring was continued for a further 2 hr at 50–60°. The mixture was then concentrated to *ca.* 350 ml under vacuum and extracted with $CHCl_3$ and dried ($MgSO_4$). The product crystallized spontaneously on evaporation of the solvent and was recrystallized from aqueous ethanol giving the nitrile **40** as colorless needles: mp 168–169° (24%); ir (Nujol) 3180, 3090, 2245 (vw), 1715 cm^{-1}; pmr δ 1.22, 1.38, 1.68 (all singlets, 3 H each), 2.25 (q, 2 H); mass spectrum, calcd mol wt, 152.20; found, 152.

Anal. Calcd for $C_8H_{12}N_2O$: C, 63.1; H, 7.9; N, 18.4. Found: C, 63.1; H, 7.9; N, 18.4.

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(26) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 120 (1950).

(27) K. C. Brannack, *J. Amer. Chem. Soc.*, 81, 3379 (1959).

(28) The procedure was essentially that of G. Cainelli, F. Bertini, P. Grasselli, and G. Zubiani, *Tetrahedron Lett.*, 5153 (1967); H. M. Frey and R. K. Sally, *Trans. Faraday Soc.*, 65, 1372 (1969).

(29) W. Nagata and M. Yoshioka, *Tetrahedron Lett.*, 1913 (1966); W. Nagata, T. Terasawa, and T. Aoki, *Chem. Pharm. Bull.*, 11, 819 (1963); H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 1866 (1966).

(30) *Chem. Abstr.*, 57, P3294*f* (1962); British Patent 887,411 (1962).

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.

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

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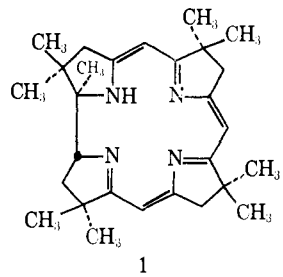
Abstract: A new, quite versatile, method for the synthesis of semicorrins is described which is based on the special utility of isoxazoles as intermediates.

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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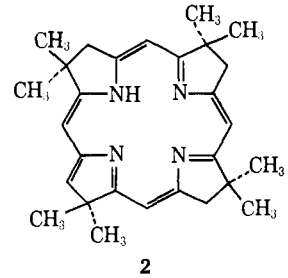

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(1) Preliminary communications: R. V. Stevens, L. E. DuPree, Jr., and M. P. Wentland, *Chem. Commun.*, 821 (1970).
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(6) (a) R. V. Stevens, C. G. Christensen, W. L. Edmonson, M. Kaplan, E. B. Reid, 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).