Studies on the Synthesis of Corrins and Related Ligands. Employment of Isoxazoles as Intermediates in the Synthesis of Semicorrins

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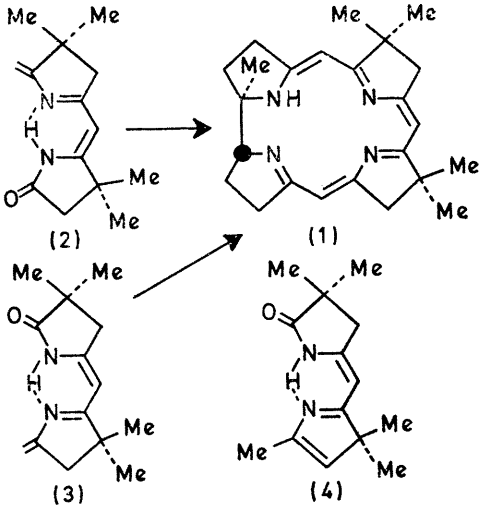
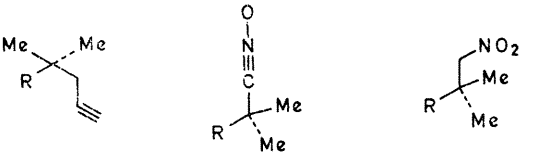
Summary A new, potentially general, method for the synthesis of semicorrins is described, based on the use of isoxazoles as intermediates.

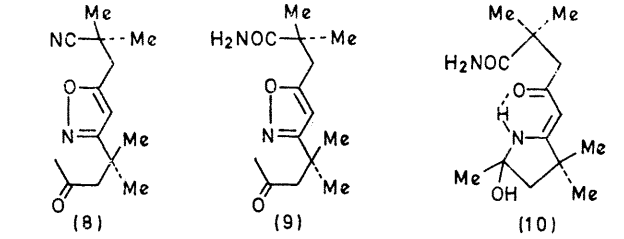
THE corrin ligand (**1**)† which serves as the basic framework for vitamin B_{12} and related natural products has recently been the subject of a number of synthetic studies.[1] We now report a simple, fundamentally different, synthetic approach to the "Eastern" or BC portion of this ring system. Of the two possible semicorrins, (**2**) and (**3**), which could conceivably be employed in a corrin synthesis, the former has already been incorporated into the macrocyclic ligand by use of transition-metal templates.[2] Our method employs isoxazoles as a scaffold for combining the essential elements of either of these semicorrinoids in a single operation.[3]

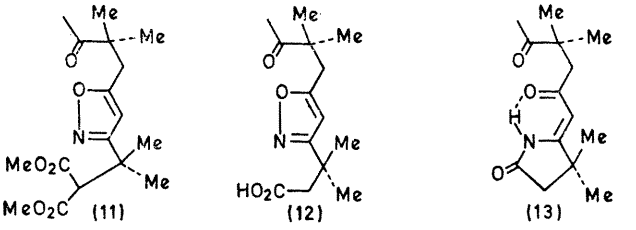


The $LiNH_2$-induced alkylation[4] of isobutyronitrile with prop-2-ynyl chloride provided the acetylenic nitrile (**5a**), b.p. 48—50°/14 mm.‡ Correct combustion and mass-spectral data were obtained on the corresponding amide, m.p. 87—87·5°. Cycloaddition of (**5a**) and the nitrile oxide (**6a**), prepared *in situ* by the $POCl_3$-induced dehydration[5] of the nitro-ketone (**7a**),[6] proceeded smoothly in refluxing $CHCl_3$ to give a 43% yield of the isoxazole (**8**): b.p. 135—138°/0·14 mm; 2,4-dinitrophenylhydrazone m.p. 139·5—140°. Alkaline hydrogen peroxide hydrolysis[7] of this nitrile quantitatively yielded the amide (**9**): m.p. 92—93°. Hydrogenolysis of this isoxazole (No. 28 active Raney nickel catalyst, 40 lb./in.², 24 hr.) gave the crude vinylogous carbinolamide (**10**) in quantitative yield: m.p. 135·5—136·5°; u.v. λ_{max} (95% EtOH) 303 nm (ε22,500). The necessary elimination of the elements of 2 equiv. of water from (**10**) was achieved in 90% yield by exposure to 2 equiv. of potassium t-butoxide in refluxing Bu^tOH for 12 hr. The crude material was conveniently purified by sublimation (60°/0·1 mm), and the resultant green-yellow needles appeared homogeneous by t.l.c. (silica) using a number of solvents and solvent systems. However, its m.p. (73—85°) suggested a possible tautomeric mixture of semicorrins (**3**) and (**4**), and this point was conclusively established from the n.m.r. spectrum which revealed an approximate ratio of 1 : 3·5 for (**3**) and (**4**),



(5) a; R = CN (6) a; R = CH_2COMe (7) a; R = CH_2COMe
b; R = COMe b; R = $CH(CO_2Me)_2$ b; R = $CH(CO_2Me)_2$





respectively: n.m.r. ($CDCl_3$) δ 1·17 (s,6), 1·30 (s,6), 2·10 (d, 2·4, *J* 1·3 Hz), 2·47)broad t, 0·4, *J* 2·0 Hz), 2·79 (d, 2, *J* 1·5 Hz), 5·10 (m,0·4), 5·21 (t, 1, *J* 1·5 Hz), and 5·53 (q, 0·8, *J* 1·3 Hz); 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); i.r. ν_{max} 3200 (broad), 1723, 1642, 1620, and 1587 cm^{-1}; u.v. λ_{max} (95% EtOH) 262 (ε 5205) and 336 nm (12,830). Having established the feasibility of this synthetic approach, we turned our attention to the alternative semicorrin (**2**).[2]

The required acetylenic ketone (**5b**) was obtained in a single step in 25% yield from the $LiNH_2$-induced alkylation

† The particular peripheral geminal substitution pattern selected in this and other[1] studies corresponds to that found in natural corrin complexes.

‡ Each intermediate or crystalline derivative thereof reported in this communication has been subjected to i.r. n.m.r., and wherever applicable, u.v. analysis. Supporting data were obtained from mass spectral and/or combustion analysis. In every instance the assigned structures are in complete accord with these data.

of isopropyl methyl ketone with prop-2-ynyl chloride in Me_2SO (2,4-dinitrophenylhydrazone m.p. 112—112·5°). The nitro-diester (**7b**) had previously been prepared[8] by conjugate addition of dimethyl malonate to nitroisobutene. The *in situ* dehydration of (**7b**) to the nitrile oxide (**6b**) and cycloaddition thereof were best achieved by slow addition of a mixture of the nitro-compound and Et_3N to a benzene solution of the acetylene and phenyl isocyanate,[9] a 95% yield of isoxazole (**11**) being obtained. Saponification of the diester and decarboxylation in refluxing toluene yielded the keto-acid (**12**). Atmospheric-pressure hydrogenolysis of a methanolic solution of this isoxazole, using active Raney nickel catalyst not only induced the expected N–O bond cleavage but was also accompanied by spontaneous cyclization to the known[10] lactam (**13**). Transformation of this compound into the semicorrin (**1**) followed the Eschenmoser procedure.

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[1] Y. Yamada, D. Miljkovic, P. Wehrli, B. Golding, P. Löliger, R. Keese, K. Müller, and A. Eschenmoser, *Angew. Chem. Internat. Edn.*, 1969, **8**, 343.

[2] A. Eschenmoser, R. Scheffold, E. Bertole, M. Pesaro, and H. Gschwend, *Proc. Roy. Soc.*, 1965, *A*, **288**, 306 and references cited therein.

[3] A paper dealing with the employment of isoxazoles as a new method of synthesis of γ-substituted butyrolactams which may be useful for the synthesis of corrin intermediates has recently appeared. G. Traverso, A. Barco, G. P. Pollini, M. Anastasia, V. Sticchi, and D. Pirillo, *Il Farmaco, Ed. Sci.*, 1969, **24**, 946; *Chem. Abs.*, 1970, **72**, 78342 u. We have independently studied the same model systems as the Italian group and will report the details of these and other examples as well as the semicorrins reported herein in a full paper.

[4] According to the procedure of Paul-Louis Compagnon and M. Miocque, *Bull. Soc. chim. France*, 1968, 2105.

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

[6] L. I. Smith and V. A. Engelhardt, *J. Amer. Chem. Soc.*, 1949, **71**, 2676.

[7] For a similar procedure see R. Q. Brewster and W. Schroeder, *Org. Syn. Coll. Vol.* **2**, 1943, 586.

[8] C. Balmer, U.S.P. 2,431,451; *Chem. Abs.*, 1948, **42**, 2615.

[9] T. Makaiyama and T. Hoshino, *J. Amer. Chem. Soc.*, 1960, **82**, 5339.

[10] E. Bertole, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem. Internat. Edn.*, 1964, **3**, 490.