Similar condensations have been observed with zinc ester enolates (Reformatsky reagents).[3] Vaughan suggested a ketene intermediate for the self-condensation of the reagent prepared from ethyl α-bromoisobutyrate and zinc metal as shown in eq 4.[4]

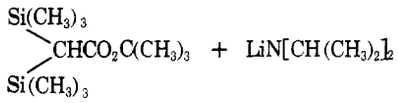
$$BrZnC(CH_3)_2CO_2C_2H_5 \rightarrow (CH_3)_2C{=}C{=}O + BrZnOC_2H_5 \quad (4)$$

$$(CH_3)_2C{=}C{=}O + BrZnC(CH_3)_2CO_2C_2H_5 \xrightarrow{H_3O^+} (CH_3)_2CHCOC(CH_3)_2CO_2C_2H_5 \quad (5)$$

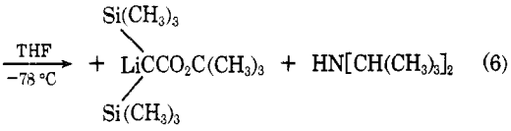
Ketene intermediates have also been proposed for the E_1CB mechanism of hydrolysis of malonic and β-keto esters.[5,6]

We report here what is to our knowledge the first isolation of a ketene from the decomposition of an ester enolate.

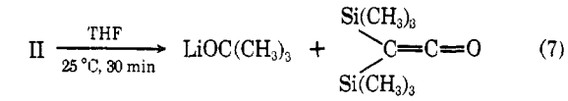
Addition of *tert*-butyl bis(trimethylsilyl)acetate, I, to an equivalent amount of lithium diisopropylamide gave the corresponding ester enolate, II (eq 6).[7] Warming solutions of



I



II to room temperature did not produce the usual yellow color indicative of ester condensation. Instead, the solution remained colorless and GLC analysis showed the presence of a single product, identified as bis(trimethylsilyl)ketene, III (eq 7). Vacuum distillation of the reaction mixture gave pure samples of III [60%, bp 20 °C (2 mm)].

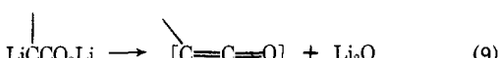


III (85%, GLC)

Bis(trimethylsilyl)ketene has previously been obtained as a side product of a Grignard synthesis of trimethylsilyl butoxyacetylene.[8] The present assignment of structure rests on a comparison of IR bands [2085, 1295 cm^{-1} (lit.[8] 2085, 1295 cm^{-1})], the ^1H NMR spectrum (CCl_4) δ 0.25(s), and ethanolysis with acidic ethanol to give ethyl bis(trimethylsilyl)acetate.[9]

The ability to isolate ketene rather than condensation product in the present case is clearly due to the steric hindrance to further reaction presented by the bulky trimethylsilyl groupings in III.[10] We are now attempting to obtain evidence for the formation of ketene intermediates in the self-condensation of simple aliphatic lithium ester enolates. We note that a ketene mechanism provides a simple explanation for the much greater stability (compared to lithium ester enolates) reported for the enolates of *N,N*-dialkylamides[11] and lithium carboxylates,[12] both of which have exceptionally poor leaving groups (eq 8, 9).

(8)



(9)

Acknowledgment is made to the National Science Foundation for partial support of this research.

References and Notes

(1) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).
(2) (a) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973); (b) L. Lochmann and D. Lim, *J. Organometal. Chem.*, **50**, 9 (1973).
(3) R. L. Shriner, *Org. React.*, **1**, 1 (1942).
(4) W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965).
(5) (a) W. A. Remero, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 2910 (1965); (b) B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.*, **91**, 2993 (1969); (c) R. F. Pratt and T. C. Bruice, *ibid.*, **92**, 5956 (1970); (d) J. Rebek, D. Brown, and S. Zimmerman, *ibid.*, **97**, 454 (1975).
(6) The lithium enolate of a 1,3-oxazine was reported to form a ketenimine on warming to 0–25 °C: A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.*, **38**, 2129 (1973).
(7) S. L. Hartzell and M. W. Rathke, *Tetrahedron Lett.*, **32**, 2737 (1976).
(8) L. L. Shchukovskaya, A. I. Koltsov, A. N. Lazarev, and R. I. Palchick, *Dokl. Akad. Nauk, SSSR*, **179**, 892 (1968).
(9) ^1H NMR spectrum (CCl_4): δ 0.23 (s, 18 H), 1.3 (t, 3 H), 1.6 (s, 1 H), 4.1 (q, 2 H).
(10) For example, III appears to be inert to the methyl Grignard reagent and reacts only sluggishly with *n*-butyllithium at 25 °C.
(11) For example, THF solutions of α-lithio-*N,N*-dimethylacetamide are stable for several days at 25 °C: R. P. Woodbury and M. W. Rathke, *J. Org. Chem.*, in press.
(12) (a) D. O. DuPree and R. D. Closson, *J. Am. Chem. Soc.*, **80**, 2311 (1958); (b) P. L. Creger, *ibid.*, **92**, 1396 (1970).

Donald F. Sullivan, Richard P. Woodbury
Michael W. Rathke*
Department of Chemistry, Michigan State University
East Lansing, Michigan 48824
Received January 20, 1977

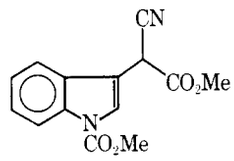
Oxazoles in Organic Chemistry. Synthesis of the Antitumor Agent Ellipticine

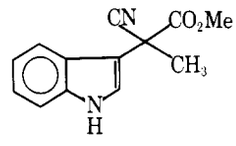
Summary: An efficient total synthesis of the alkaloid ellipticine through the intermediacy of a substituted oxazole has been achieved. The versatility of this intermediate for the preparation of peripherally modified analogues is emphasized.

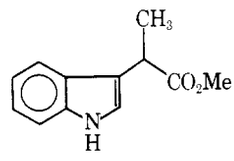
Sir: The chemistry of oxazoles was first seriously investigated when the antibiotic penicillin was believed to contain this heterocyclic moiety.[1] More recently, the Diels–Alder reaction of substituted oxazoles has been found to provide a convenient method for the preparation of pyridoxine (vitamin B_6) and its analogues and homologues.[2] The azadiene component of the oxazole generally condenses with a dienophile in a highly regiospecific fashion to furnish a substituted pyridine base of the isonicotinic acid series (the electron-withdrawing group of the dienophile assumes position 4 of the pyridine ring[3]).

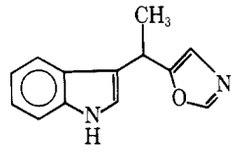
Our interest in the development of a general strategy for the preparation of several therapeutically important alkaloids led us to further pursue the chemistry of this class of heterocycles. Ellipticine (**6**), an alkaloid present in plants of genera *Ochrosia* and *Aspidosperma*, has stimulated numerous synthetic efforts because of its potent antitumor activity.[4] We chose this molecule as the first simple target in our pursuit of a general oxazole based strategy for alkaloid synthesis.

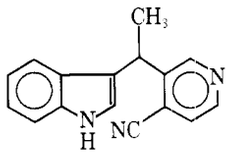
The key intermediate in our planned scheme, the 5-substituted oxazole **4**, was synthesized starting from gramine. Thus, following a general method for the preparation of indolyl aliphatic acids reported by Suvorov,[5] indoleacetonitrile (from gramine, KCN, CH_3I)[6] was dicarbomethoxylated (dimethyl carbonate, NaOMe, benzene) to give **1**. Further treatment with NaOMe/CH_3I proceeded with loss of the *N*-carbomethoxy group and C-methylation to yield the re-

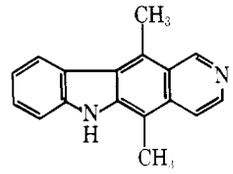

1


2


3


4


5


6

ported product **2**, which on hydrolysis, decarboxylation, and esterification provided methyl 2-(3-indolyl)propionate (**3**) in 74% yield (KOH–ethylene glycol at 195 °C, 13 h, then refluxing methanol with acid-washed AG 50W-X2 as catalyst, 6 h).[7] Reaction of this ester with excess α-lithiated methyl isocyanide ($LiCH_2N{\equiv}C$, 4 equiv, −50 °C) followed by warming to 0 °C and quenching with acetic acid provided the crystalline oxazole **4** (80% yield after silica gel chromatography, mp 74–75 °C).[8] Diels–Alder reaction of **4** with excess acrylonitrile in acetic acid at 145 °C for 24 h gave 3-[1-(indol-3-yl)ethyl]pyridine-4-carbonitrile (**5**) in 16% yield after two successive chromatographic purification: NMR ($CDCl_3$) δ 8.66 (d, 1 H, J = 2 Hz), 8.56 (d, 1 H, J = 6 Hz), 8.25 (br s, 1 H), 7.48–6.96 (m, 6 H), 4.74 (q, 1, J , 9 Hz), 1.79 (d, 3 H, J = 9 Hz).

The synthesis of ellipticine is formally completed at the stage for the same pyridinecarbonitrile **5** was recently prepared by Sainsburg and Schinazi by another route and converted in two additional steps to the target molecule.[9] Thus, following their procedure, addition of methyllithium to **5** (4 equiv) followed by hydrolysis and cyclization with 20% acetic acid gave a yellow solid in 80% yield whose spectral and physical properties were in accord with those reported for ellipticine.[9]

Although the yield in the Diels–Alder reaction is somewhat low,[10] the simplicity of the overall scheme makes our synthesis competitive with existing methods. In addition, since analog studies have revealed that skeletal modifications of ellipticine diminish its antitumor activity, the generation of chemical variants has focused on peripheral modifications of the parent molecule.[11] The oxazole based strategy should permit easy access to analogues containing peripherally modified D rings, for either the α-metallated isonitrile used to generate the oxazole or the dienophilic component employed in the Diels–Alder reaction is readily varied.

Such modifications will be the subject of a future communication. The application of oxazoles to the synthesis of benzylisoquinolines and benzazepines has also been accomplished, and will be reported separately.[12]

Acknowledgment. We are indebted to the Petroleum Research Foundation, administered by the American Chemical Society, Health Research and Services Foundation (HRSF) of Pittsburgh, Pa., and the National Institutes of Health for support of these investigations. N.M.H. also expresses his gratitude to the Fulbright–Hays Committee for a fellowship.

References and Notes

(1) J. W. Cornforth in "The Chemistry of Penicillin", H. T. Clarke, J. R. Johnson, and R. Robinson, Ed, Princeton University Press, Princeton, N.J., 1949, Chapter 21, pp 688–730.
(2) E. E. Harris, R. A. Firestone, K. Pfister, R. R. Boettcher, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson, and W. Reuter, *J. Org. Chem.*, **27**, 2705 (1962); R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron*, **23**, 943 (1967); P. F. Muhlradt, Y. Marino, and E. E. Snell, *J. Med. Chem.*, **10**, 341 (1967).
(3) M. Ya Karpeiskii and V. L. Florent'ev, *Russ. Chem. Rev.*, **38**, 540 (1969).
(4) R. B. Woodward, G. A. Iacobucci, and F. A. Hochstein, *J. Am. Chem. Soc.* **81**, 4434 (1959); P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 3482 (1962); K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Aust. J. Chem.*, **20**, 2715 (1967). For syntheses of the structurally related alkaloid, olivacine, see T. Kametani, T. Suzuki, Y. Ichikawa, and K. Fukumoto, *J. chem. Soc., Perkin Trans. 1*, 2102 (1975); E. Wenkert and K. G. Dave, *J. Am. Chem. Soc.*, **84**, 94 (1962); J. P. Kutney and D. S. Grierson, *Heterocycles*, **3**, 171 (1975); C. W. Mosher, O. P. Crews, E. M. Acta, and L. Goodman, *J. Med. Chem.*, **9**, 237 (1966).
(5) V. S. Rozhkov, Y. I. Smushkevich, and N. N. Suvorov, *J. Heterocycl. Chem.*, **11**, 826 (1976).
(6) H. B. Henbest, E. R. H. Jones, and G. F. Smith, *J. Chem. Soc.*, 3796 (1953).
(7) P. J. Mill and W. R. C. Crimmin, *Biochim. Biophys. Acta*, **23**, 432 (1957); N. N. Suvorov, B. Ya. Eryshev, L. E. Frumin, and A. G. Dubinin, *J. Heterocycl. Chem.*, **10**, 1325 (1976).
(8) U. Schöllkopf and R. Schröder, *Angew Chem., Int. Ed. Engl.*, **10**, 333 (1971).
(9) M. Sainsbury and R. F. Schinazi, *J. Chem. Soc., Perkin Trans. 1*, 1155 (1976); K. N. Kilminster and M. Sainsbury, *ibid.*, 2264 (1972); K. N. Kilminster, M. Sainsbury, and B. Webb, *Phytochemistry*, **11**, 389 (1972).
(10) No systematic attempts to optimize this yield have been made. Preliminary experiments, however, do indicate that acrylic acid should allow substantial improvement in the yield of an appropriately functionalized pyridine base. Satisfactory spectral and physical data were obtained for all new compounds.
(11) R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullin, and R. W. Kierstead, *J. Med. Chem.*, **18**, 755 (1975).
(12) A. P. Kozikowski and N. Schulz, in preparation.

Alan P. Kozikowski,* Naim M. Hasan
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Received March 3, 1977