attempted under a variety of conditions without evidence of any of the desired ring opening. This molecule is highly sterically hindered, and nucleophilic ring-opening reactions (methyl Grignards, methyllithium, dimethylcopper lithium) have all been found to fail. A similar failure was found for the ring-opening of tetraphenylethylene oxide.

With this additional background one can now postulate a reasonable sequence of events for the reductive ring-opening reactions of epoxides with morpholine–borane and boron trifluoride. The boron trifluoride is clearly required to complex with the epoxide oxygen as well as to tie up the morpholine in the borane complex. If the epoxide can ring open to give a relatively stable carbocation, then reduction may give the less substituted alcohol with attack of the reducing agent occurring from the side of the incipient hydroxyl function as reported for 1-phenylcyclohexene oxide.[2] If the carbocation has less stability, as in the case of 1-methylcyclohexene oxide, the borane attacks not the free ion but the complexed epoxide with inversion of configuration at the tertiary center. Styrene oxide can form a relatively stable cation and 2-phenylethanol results. Epichlorohydrin and 2,3-epoxypropyl *p*-methoxyphenyl ether have electronegative groups on the methylene attached to the epoxide ring. These destabilize the system for carbocation formation at the more highly substituted ring carbon. Consequently, the hydride is delivered to the least sterically hindered terminal position in these molecules.

Experimental Section

All chemicals were obtained from Aldrich and used as received. The oxide from 1-methylcyclohexene was made in the usual fashion from the olefin and *m*-chloroperbenzoic acid. The same reaction was utilized to produce the epoxide from 2-ethyl-1-hexene.[6] Proton NMR spectra were taken on a Varian EM 390 instrument in deuteriochloroform solution by using Me_4Si as an internal standard. Carbon-13 NMR were taken on a JEOL FX-60 instrument operating at 15 MHz and using 8K transforms. Identification of all compounds was by a combination of TLC and proton and carbon-13 NMR using comparisons with a variety of standard compounds. Whenever possible quantification was by means of integrating of the proton NMR spectrum. However, it was often best to use the peak intensities of selected lines in the carbon spectrum. Since the product molecules were all of the same size by using methylene carbons, differences in relaxation effects are small or nil. From standard mixes it is estimated that analyses carried out in this fashion are good to 5% to 10% which was considered good enough for this study.

Reactions of Epoxides with Morpholine–Borane. A mixture of 5 mmol of the epoxide and 5 mmol of morpholine–borane in 30 mL of anhydrous ether was stirred at room temperature while 5 mmol of boron trifluoride etherate in 20 mL of ether were added dropwise. The reaction was stirred for 2 h and then poured into 50 mL of dilute hydrochloric acid. The ether layer was drawn off, and the acid layer was extracted with two small portions of methylene chloride. The combined organic layers were dried (anhydrous sodium sulfate) and filtered, and the solvent was removed on a rotary evaporator. Except where mentioned in the text, the yields of crude product weighed from 100% to 110% of the expected weight for 100% theoretical yield. In those cases where the weight was high, it was invariably found that the balance was due to unreacted morpholine–borane. The one exception to these statements was epichlorohydrin where the recovered material was only 80% of the expected. It was presumed that this was due to the water solubility of the propylene chlorohydrin product.

The following epoxides gave results discussed in the text: styrene oxide, 1-methylcyclohexene oxide, 2-ethyl-1-hexene oxide, epichlorohydrin, and 2,3-epoxypropyl *p*-methoxyphenyl ether. Norbornene oxide gave a very complex set of products which did not include the expected norbornols but appeared to indicate incorporation of morpholine in the product. As mentioned in the text, the epoxide of 1-butene gave a mixture which appeared to contain borate esters. The syn epoxide of 5,8-diacetoxy-1,4-dihydro-1,4-ethanonaphthalene did not react at all nor did tetraphenylethylene epoxide.

Ancillary Experiments. (a) A solution of 0.56 g (5 mmol) of 1-methylcyclohexene oxide in 10 mL of ether was treated with 0.63 g of boron trifluoride etherate at room temperature for 2 h. The solution was poured into water and the ether layer separated. The aqueous layer was extracted twice with small portions of ether. The combined ether extracts were evaporated to yield 0.43 g of oil with the proton and carbon-13 spectra of standard pure samples of 2-methylcyclohexanone. (b) In a series of three experiments, 0.56 g (5 mmol) of 2-methylcyclohexanone in 30 mL of ether was treated with (1) 0.53 g of morpholine–borane; (2) 0.53 g of morpholine–borane and then 0.63 g of boron trifluoride etherate; and (3) 5 mL of 1 M boron hydride in THF. Each of the experiments was allowed to stand for 2 h and then worked up as above. Yields and percent of *trans*-2-methylcyclohexanol were as follows (the balance of the product was *cis*-2-methylcyclohexanol): (1) 0.67 g, 83%; (2) 0.60 g, 86%; and (3) 0.69 g, 83%.

Acknowledgment. Grateful acknowledgment is hereby extended to the Robert A. Welch Foundation for their support of this work.

Registry No. $Ph(CH_2)_2OH$, 60-12-8; $CH_3CH(OH)CH_2Cl$, 127-00-4; styrene oxide, 96-09-3; 1-methylcyclohexene oxide, 1713-33-3; 2-ethyl-1-hexene oxide, 1436-35-7; epichlorohydrin, 106-89-8; 2,3-epoxypropyl *p*-methoxyphenol ether, 2211-94-1; norbornene oxide, 278-74-0; 1,2-epoxybutane, 106-88-7; 5,8-diacetoxy-1,4-dihydro-1,4-ethanonaphthylene syn epoxide, 86557-37-1; tetraphenylethylene epoxide, 470-35-9; morpholine–borane, 4856-95-5; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; 1-methylcyclohexanol, 590-67-0; 2-methylcyclohexanone, 583-60-8; 2-ethyl-1-hexanol, 104-76-7; 1-(*p*-methoxyphenoxy)-2-propanol, 42900-54-9; boron trifluoride etherate, 109-63-7; boron hydride, 11129-13-8.

(6) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112.

Total Synthesis of Leucoxylonine

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Received November 29, 1983

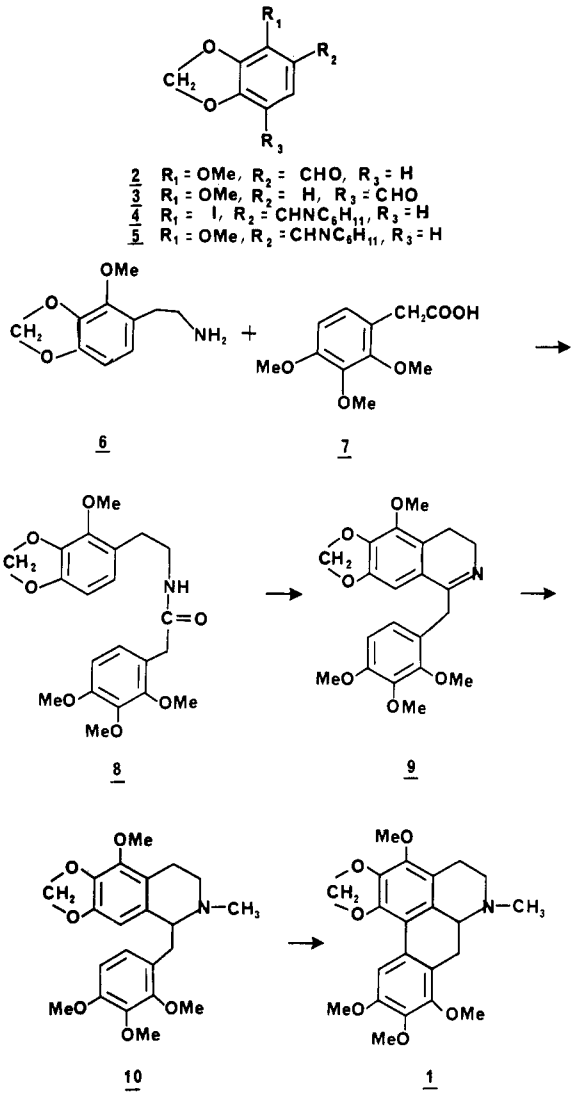
Leucoxylonine was first isolated[1] in 1960 from *Ocotea leucoxylon* (Lauraceae), but its structure was not determined until 1977 when it was reisolated and assigned structure **1** essentially on the basis of spectral data.[2] Leucoxylonine was the first known nonphenolic hexaoxygenated aporphine. Herein we describe a total synthesis of leucoxylonine which unambiguously confirms the assigned structure **1** for the alkaloid.

The scheme formulated for the synthesis of **1** (Scheme I) required the initial synthesis of 2-methoxy-3,4-(methylenedioxy)benzaldehyde (**2**). The usual method[3] for the preparation of this aldehyde involves a two-step conversion of *o*-vanillin to 1-methoxy-2,3-(methylenedioxy)benzene which, on formylation, gives the aldehyde **2** (in 46% yield) together with its isomer, 4-methoxy-2,3-(methylenedioxy)benzaldehyde (**3**) in comparable yield. The following new procedure was devised for the synthesis of **2** in order

(1) Goodwin, S.; Smith, A. F.; Horning, E. C. *Chem. Ind. (London)* **1960**, 691.
(2) Ahmad, R.; Cava, M. P. *Heterocycles* **1977**, *7*, 927.
(3) Govindachari, T. R.; Rajadurai, S.; Ramadas, C. V.; Viswanathan, N. *Chem. Ber.* **1969**, *93*, 360 and references cited therein.

0022-3263/84/1949-3220$01.50/0

Scheme I



to avoid the previously necessary laborious chromatographic separation of **2** and **3**.

Cuprous iodide is known to catalyze the nucleophilic substitution of a number of aryl bromides or iodides by methoxide ion.[4] These CuI-catalyzed reactions were widely applicable for conversions of the type $C_6H_4XBr \rightarrow C_6H_4XOMe$ and gave the highest yields when X was an alkyl, alkoxy, or carboxy group.[4] The CuI-catalyzed reaction has now been employed for a convenient synthesis of the aldehyde **2**. Thus, when 2-iodo-3,4-(methylenedioxy)benzaldehyde cyclohexylimine **4** (readily prepared from piperonal[5]) was treated with excess sodium methoxide in refluxing methanol in the presence of a catalytic amount of CuI, 2-methoxy-3,4-(methylenedioxy)benzaldehyde cyclohexylimine **5** was obtained in quantitative yield. Imine **5** was then readily hydrolyzed to aldehyde **2**.

Conversion of **2** to β-(2-methoxy-3,4-(methylenedioxy)-phenyl)ethylamine (**6**),[3] followed by reaction of **6** with (2,3,4-trimethoxyphenyl)acetic acid (**7**)[6] in the presence of *N*-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroisoquinoline[7] (EEDQ) gave the phenylacetamide **8**. Bischler–Napieralski cyclization[8] of the amide **8** gave the dihydrobenzylisoquinoline **9**. The 1,2,3,4-tetrahydrobenzylisoquinoline **10** formed by N-methylation and selective reduction of product **9** was then oxidatively cyclized by using thallium(III) trifluoroacetate (TTFA)[9] to give **1**, having identical spectral properties with leucoxylonine from natural sources.

Experimental Section

Melting points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories and Midwest Microlab Ltd. IR spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ solution on a Bruker WM-250 (250 MHz) spectrometer with Me_4Si as the reference. Mass spectra were taken on either a Hitachi-Perkin-Elmer RMH2 mass spectrometer or a V. G. Micromass 7070H mass spectrometer.

2-Iodo-3,4-(methylenedioxy)benzaldehyde cyclohexylimine (4) was prepared from piperonal according to the procedure of Ziegler and Fowler.[5] Recrystallization from methanol gave **4** as colorless prisms, mp 167–168 °C (lit.[5] mp 167–168.5 °C).

2-Methoxy-3,4-(methylenedioxy)benzaldehyde Cyclohexylimine (5). Cuprous iodide (1.4 g, 1.0 mol) and **4** (130 g, 0.364 mol) were added to a solution of sodium methoxide (70 g, 1.30 mol) in methanol (2000 mL) and the mixture was refluxed for 16 h. Water (200 mL) was added and the mixture was filtered. The filtrate was concentrated and **5** crystallized out as bright yellow needles (95.0 g, 94%): mp 102–104 °C; IR (KBr) 2901, 1605, 1070, 823 cm^{-1}, HRMS, *m/e* 261.1375 (M^+); calcd for $C_{15}H_{19}NO_3$ 261.1377.

2-Methoxy-3,4-(methylenedioxy)benzaldehyde (2). Aqueous 10% HCl (200 mL) was added to a stirred solution of **5** (80.0 g, 0.310 mol) in CH_2Cl_2 (500 mL). The mixture was stirred for 6 h and on workup gave pale yellow needles of **2** (51.5 g, 92%): mp 101–102 °C (lit.[3] mp 103–105 °C); IR (KBr) 1613 cm^{-1}. **β-(2-Methoxy-3,4-(methylenedioxy)phenyl)ethylamine (6)** was prepared from **2** as described by Govindachari et al.[3] The oily amine was stored as the oxalate, mp 174–175 °C (lit.[10] mp 173–175 °C).

***N*-(2-Methoxy-3,4-(methylenedioxy)phenethyl)-2-(2,3,4-trimethoxyphenyl)acetamide (8).** The amine **6** was liberated from its oxalate (0.5 g, 1.75 mmol) by treatment with NH_4OH and extraction with benzene. The dried benzene extract (35 mL) was added to a solution of (2,3,4-trimethoxyphenyl)acetic acid (**7**; 0.4 g, 1.75 mmol) and EEDQ (0.5 g, 2.0 mmol). The mixture was stirred at room temperature overnight, the solvent was partly removed, and the precipitated solid (0.62 g, 89%) was removed by filtration. Recrystallization from benzene–hexane gave colorless needles of the amide **8**: mp 95 °C; IR (KBr) 1640 cm^{-1}; ^1H NMR δ 6.86, 6.62, 6.45, 6.38 (4 d, *J* = 8.0 Hz, 4 H, 4 Ar H), 5.90 (s, 2 H, OCH_2O), 5.89 (br s, 1 H, NH), 3.91, 3.86, 3.84, 3.81 (4 s, 12 H, 4 OCH_3), 3.44 (s, 2 H, CH_2Ar), 3.36 (t, *J* = 6.6 Hz, 2 H, CH_2CH_2N-), 2.65 (t, *J* = 6.6 Hz, 2 H, CH_2CH_2N-); MS, *m/e* 403 (M^+). Anal. Calcd for $C_{21}H_{25}O_7N$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.65; H, 6.29; N, 3.67.

1-(2,3,4-Trimethoxybenzyl)-5-methoxy-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (9). A mixture of amide **6** (0.25 g, 0.62 mmol), acetonitrile (6.0 mL), and phosphorus oxychloride (0.5 mL, 5.4 mmol) was refluxed for 90 min, when TLC indicated no starting material. The reaction mixture was cooled, and absolute ethanol (8 drops) was added dropwise to destroy excess $POCl_3$. The mixture was concentrated under vacuum, diluted with water, basified with ammonium hydroxide, and extracted with dichloromethane. Removal of solvent gave a gum which later gave an amorphous yellow solid (0.239 g, 95%): mp 107 °C; ^1H NMR δ 6.84 (d, *J* = 9.5 Hz, 1 H, ArH), 6.80 (s, 1 H, ArH), 6.56 (d, *J* = 9.5 Hz, 5.90 (s, 2 H, OCH_2O), 3.97 (s, 3 H, OCH_3), 3.93 (s, 2 H, CH_2Ar), 3.90, 3.87, 3.81 (3 s, 9 H, 3 OCH_3), 3.63 (t, *J* = 7.4 Hz, 2 H), 2.61 (t, *J* = 7.4 Hz, 2 H. Anal. Calcd for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02; N, 3.63; Found: C, 65.50; H, 5.96; N, 3.92.

1-(2,3,4-Trimethoxybenzyl)-5-methoxy-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (10). A solution

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(5) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.
(6) Lenz, G. R.; Woo, C. *J. Heterocycl. Chem.* **1981**, *18*, 691.
(7) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651.
(8) Teitel, S.; Brossi, A. *J. Heterocycl. Chem.* **1968**, *5*, 825.
(9) Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; McKillop, A. *J. Am. Chem. Soc.* **1980**, *102*, 6513.
(10) Cava, M. P.; Libsch, S. S. *J. Org. Chem.* **1974**, *39*, 577.

of **9** (210 mg, 0.545 mmol) in 10 mL of methanol was stirred under nitrogen with 1 mL 37% formalin at room temperature for 30 min. Sodium borohydride (400 mg) was added and the solution was stirred for an additional 1 h. The solvent was removed under vacuum, water was added, and the mixture was extracted with dichloromethane. The organic extract was dried (Na_2SO_4) and then evaporated to give a residue gum (190 mg), which was purified by preparative TLC ($CHCl_3$:EtOAc, 3:1) to give 65 mg (30%) of pure **10** as a gum: ^1H NMR ($CDCl_3$) δ 6.76, 6.58 (2 d, J = 8.4 Hz, 2 H, 2 Ar H); 5.97 (s, 1 H, Ar H), 5.83, 5.82 (2 s, 2 H, OCH_2O), 3.99, 3.87, 3.84 (3 s, 12 H, 4 OCH_3), 2.44 (s, 3 H, NCH_3). This material was used directly for the coupling reaction without additional characterization.

Leucoxylonine (1). A solution of **10** (40 mg, 0.10 mmol) in 1.5 mL of CCl_4 and 0.5 mL of BF_3·Et_2O was added all at once to a cooled (0 °C) solution of thallium(III) trifluoroacetate (TTFA) (75 mg, 0.14 mmol) in CH_3CN (10 mL) and CCl_4 (1.5 mL) under nitrogen. The reaction mixture was allowed to warm to room temperature and then stirred for a further 2 h. Solvent was removed under reduced pressure, water was added, and the aqueous solution was extracted with CH_2Cl_2 after the solution had been adjusted to pH 9 with NH_4OH. The organic extract was dried (Na_2SO_4) and then evaporated under vacuum to give a dark gum (26 mg). Purification by preparative TLC ($CHCl_3$:$CH_3COOC_2H_5$, 3:1) gave synthetic leucoxylonine as a gum (R_f 0.13–0.2, 10 mg. 20%). The spectral data for the synthetic leucoxylonine were identical with those reported for the natural product:[2] ^1H NMR δ ($CDCl_3$) 7.42 (s, 1 H, Ar H), 6.07, 5.91 (2 d, J = 13 Hz, OCH_2O), 4.01, 3.91, 3.90, 3.86 (4 s, 12 H, 4 OCH_3), 2.56 (s, 3 H, NCH_3); HRMS, m/e 399.1720 (M^+); calcd for $C_{22}H_{25}NO_6$ 399.1717.

Acknowledgment. We thank the University of Ibadan, Nigeria, for a research leave to A.A.A.

Registry No. (±)-1, 91199-16-5; 2, 5779-99-7; 4, 58343-44-5; 5, 91129-06-5; 6, 2220-19-1; 6·oxalate, 91129-10-1; 7, 22480-91-7; 8, 91129-07-6; 9, 91129-08-7; (±)-10, 91129-09-8; piperonal, 120-57-0.

3-Alkoxypyrroles by Reduction of Alkoxypyrrolinones[1]

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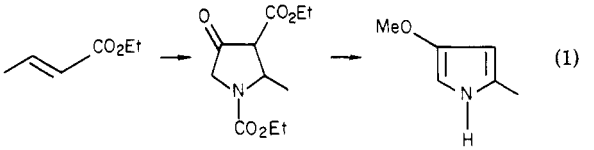
Received July 5, 1983

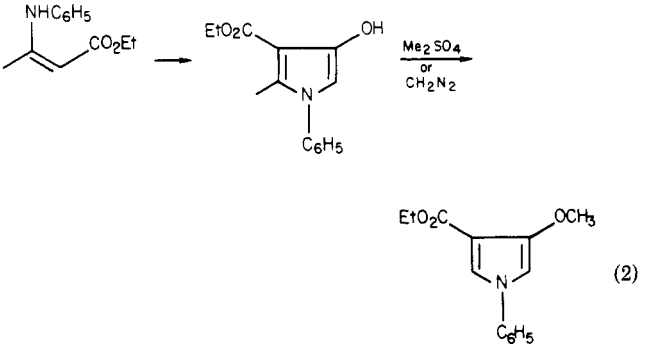
There has been tremendous interest in the chemistry of pyrroles for many years.[2] The isolation of the natural product prodigiosin, a pigment having antibiotic activity, stimulated work in 3-alkoxypyrrole synthesis and resulted in the successful preparation of this compound and various analogues.[3]

Basically, there are four methods for the generation of 3-alkoxypyrroles. Rapoport's elegant synthesis of prodigiosin[3b] used chemistry of Kuhn and Osswald.[3a,4] An initial conjugate addition to an unsaturated ester followed by Dieckmann condensation, hydrolysis, ketal formation, and dehydrogenation gives the 3-methoxypyrrole (eq 1).



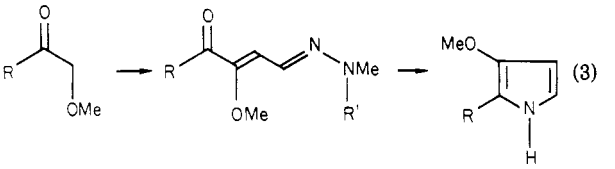
(1)

Campaigne[3d] used a similar sequence to prepare 3-alkoxy-5-arylpyrroles. A second method uses enamino esters derived from ethyl acetoacetate which are acylated with chloroacetyl chloride followed by a Dieckmann ring closure to give 3-hydroxypyrroles which can be O-methylated (eq 2).[5] Similarly, Bauer[3c] formed enamino esters from β-keto



(2)

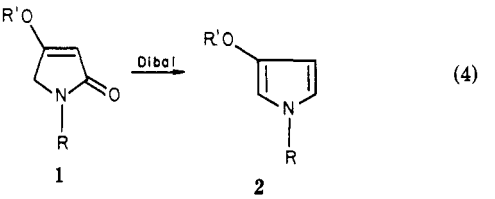
esters and ethyl glycinate and then obtained 3-alkoxypyrroles after a Dieckmann step and O-alkylation.[6] The approach of Severin[7] involves the condensation of α-methoxy ketones with glyoxalmonohydrazones followed by reduction with sodium dithionite to give 3-methoxypyrroles (eq 3). One last preparation of limited scope uses the



(3)

base-catalyzed addition of methanol to 3,4-dinitropyrroles as a key step followed by elimination of methanol.[8]

We report a new and efficient method for the preparation of 3-alkoxypyrroles (eq 4). Thus, the 4-alkoxy-Δ^3-



(4)

1 2

pyrrolin-2-ones **1**,[9] readily available from β-keto esters (see Experimental Section), are simply allowed to react with

(1) Presented in part at the 17th Middle Atlantic Regional Meeting of the American Chemical Society, April 6-8, 1983, White Haven, PA, Abstract No. 332.

(2) For example, see: "The Chemistry of Pyrroles"; Jones, R. A., Bean, G. P., Eds.; Academic Press: New York, 1977.

(3) (a) Rapoport, H.; Willson, C. D. *J. Am. Chem. Soc.* **1962**, *84*, 630. (b) Rapoport, H.; Holden, H. G. *Ibid.* **1962**, *84*, 635. (c) Bauer, H. *Liebigs Ann. Chem.* **1970**, *736*, 1. (d) Campaigne, E.; Shutske, G. M. *J. Heterocycl. Chem.* **1976**, *13*, 497.

(4) Kuhn, R.; Osswald, G. *Chem. Ber.* **1956**, *89*, 1423.

(5) (a) Benary, E.; Silberman, B. *Chem. Ber.* **1913**, *46*, 1363. (b) Benary, E.; Konrad, R. *Ibid.* **1923**, *56*, 44.

(6) Other workers had performed the same sequence of reactions but had postulated that the initial step formed an imino ester: Triebs, A., Ohorodnik, A. *Liebigs Ann. Chem.* **1958**, *611*, 139, 149.

(7) Severin, T.; Poehlmann, H. *Chem. Ber.* **1977**, *110*, 491. Severin, T.; Supp, W.; Manninger, G. *Ibid.* **1979**, *112*, 3013.

(8) Bonaccina, L.; Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1979**, *44*, 4420.

(9) These compounds are readily available from β-keto esters. Kochhar, K. S.; Carson, H. J.; Clouser, K. A.; Elling, J. W.; Gramens, L. A.; Parry, J. L.; Sherman, H. L.; Braat, K.; Pinnick, H. W. *Tetrahedron Lett.*, in press (see Experimental Section). Elaboration of ethyl acetoacetate via the monoanion or the dianion leads to a wide variety of the unsaturated lactams **1**.