weak singlet appearing at δ 2.92 ppm has been assigned to the resonance of the *N,N*-dimethyl protons of the open-chain hydrochloride salt, structure **2**. The intensity of this signal is ~8% as great as that of the major *gem*-dimethyl proton signal at δ 3.41 ppm and is consistent with the percentage of **2** calculated from ir spectral data. The upfield shift of this signal relative to the NCH_3 signals for the quaternary compounds considered here can be explained by localization of the positive charge predominantly on the proton bonded to the tertiary nitrogen.[6] As a result of this charge distribution, the deshielding of the NCH_3 protons is less for species **2** than for the quaternary compounds.

Identification of the major component present in the hydrochloride salt of **1** can be made by comparison of chemical shift data for this compound and the free carbodiimide base **1** (Figure 1B, Table I). In the spectrum of the hydrochloride salt of **1**, the partially obscured triplet centered at δ 3.48 ppm can be assigned to the signal for the e protons since $\Delta_{1\rightarrow 1HCl}\delta_f = \Delta_{1\rightarrow 1HCl}\delta_e = 1.20$ ppm. The low field triplet at δ 3.86 ppm can then be assigned to the c proton signal. A comparison of the spectra of **1** and the hydrochloride salt of **1** also shows that $\Delta_{1\rightarrow 1HCl}\delta_b = -0.09$ ppm and $\Delta_{1\rightarrow 1HCl}\delta_c = 0.59$ ppm. Using these relative chemical shift data, we have assigned **4** as the predominant species present in the hydrochloride salt of **1** for the following reasons. First, the deshielding effect of N-1 in structure **4** is expected to be greater than that of the carbodiimino nitrogen of **1**, resulting in a downfield shift for the c proton signal.[7] Second, the deshielding effect of the amino nitrogen of **4** is expected to be less than that of the carbodiimino nitrogen of **1**, resulting in an upfield shift for the b proton signal. In the case of structure **5**, one would predict the signal for the b protons to occur downfield, and the c proton signal upfield, relative to the corresponding signals for compound **1**.

Nmr spectra were also recorded for the free carbodiimide base **1** in neat phase and as a solution in chloroform. In both cases, the observed chemical shifts and coupling constants were consistent with an open chain carbodiimide structure.

In summary, the ir and nmr studies presented here demonstrate that the hydrochloride salt of **1** in water at neutral pH exists as a mixture of two isomeric forms: 7.4% as **2** and 92.6% as **4**. The methiodide derivative **3** and the free base **1** exist only as open-chain carbodiimide structures.

Experimental Section[8]

The hydrochloride salt of 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide (**1**) with uncorrected mp 109–110° (lit.[3] mp 114–115°) was purchased from the Ott Chemical Co. (Muskegon, Mich.). The derivative 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide methiodide (**3**) with uncorrected mp 90–93° (lit.[3] mp 106.5–107.5°) was prepared from freshly distilled carbodiimide base **1** and methyl iodide.[3] Structure **3** and the hydrochloride salt of **1** in 50% methanol–50% acetone move on silica gel as single bands with R_f values of 0.65 and 0.71, respectively. Only trace amounts of impurities are present. The spectra of these compounds in water and as Nujol mulls demonstrate the absence of urea bands in the 1530–1680-cm^{-1} range. As determined from the absorbance at 2128 cm^{-1}, the hydrolysis of these compounds in water at neutral pH follows first-order kinetics. At 37°, the $t_{1/2}$ for hydrolysis of the hydrochloride salt of **1** is 60 hr, and for hydrolysis of **3** it is 26 hr.

Registry No.—**1**, 1892-57-5; **2**, 25952-53-8; **3**, 22572-40-3.

(6) J. M. George, L. B. Kier, and J. R. Hoyland, *Mol. Pharmacol.*, **7**, 328 (1971).

(7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon, Oxford, England, 1969, pp 80, 81.

(8) Melting points were measured on a Thomas-Hoover apparatus. Ir spectra were recorded on a Perkin-Elmer Model 421 spectrometer. Spectra of solutions were obtained using matched 0.018-mm CaF_2 cells. Because of the weak absorbance of the hydrochloride salt of **1** at 2128 cm^{-1}, measurements at this frequency in aqueous solution were made by recording the transmittance at 5× scale expansion. Nmr spectra were recorded at ambient temperature on a Varian A-60A spectrometer.

A Facile Synthesis of 4-Substituted 3a,4,5,9b-Tetrahydrobenz[*e*]isoindolines

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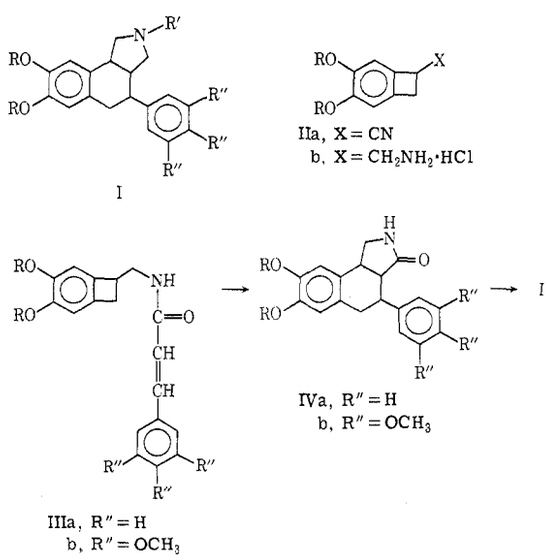
As part of our general structure–activity study of biologically active compounds,[1] synthesis of a series of 4-aryl-substituted 7,8-dialkoxy-3a,4,5,9b-tetrahydrobenz[*e*]isoindolines (I) was needed. Compounds of this type may be prepared by an Oppolzer reaction.[2] Although this route has been studied, certain required unsaturated amines may not be readily accessible and thus preclude its becoming a practical route. An alternate route has therefore been proposed. This involves direct reduction of the nitrile IIa to the amine IIb, treatment of the latter with the acid chloride of an appropriate α,β-unsaturated acid, and thermal cyclization of the resulting amide III to the α-lactam IV. The desired product I can be obtained from IV.



Since α,β-unsaturated acids are readily available and each of the aforementioned steps are convenient, high yield conversions, our method provides a useful route to compounds of this type. As an example, synthesis of 7,8-dimethoxy-2-ethyl-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]isoindoline (I, R = CH_3; R′ = C_2H_5; R″ =

(1) K. Y. Zee-Cheng and C. C. Cheng, *J. Pharm. Sci.*, **59**, 1630 (1970).

(2) W. Oppolzer, *J. Amer. Chem. Soc.*, **93**, 3833 (1971).

H) is described as follows. Treatment of 2-bromo-4,5-dimethoxyphenylpropionitrile, prepared from 3,4-dimethoxycinnamonitrile, with potassium in liquid ammonia gave a 74% yield of 1-cyano-4,5-dimethoxybenzocyclobutene[3] (IIa, R = CH_3), mp 83–84° Reduction of IIa (R = CH_3) with diborane in tetrahydrofuran[4] afforded an 85% yield of the amine IIb (R = CH_3), the hydrochloride of which melted at 201–203°. The amide IIIa (R = CH_3), mp 138–138.5°, was prepared from the amine IIb (R = CH_3) and cinnamoyl chloride in pyridine in 92% yield. A toluene solution of the amide IIIa (R = CH_3) heated at 200° for 47 hr resulted in 63% yield of the lactam IVa (R = CH_3), mp 249–250°. (Analysis of the toluene mother liquor by tlc showed at least five spots; these by-products were not studied at the present time.) The ir spectrum of the unsaturated amide IIIa (R = CH_3) showed a carbonyl stretching absorption at 1650 and a double-bond stretching absorption at 1620 cm^{-1}; the rearranged isomeric product IVa (R = CH_3) showed a carbonyl absorption at 1695 cm^{-1}, consistent with the γ-lactam assignment. No vinyl protons appeared in the pmr of IVa (R = CH_3). Regrettably, the methine and methylene proton signals did not provide enough information for stereochemical assignments.

The mass spectra of compounds IIIa (R = CH_3) and IVa (R = CH_3) showed that the molecular ion has the same mass in both cases [*m/e* 323 (M^+)]; yet the stability of the ionized molecules differ greatly. The molecular ion of IIIa (R = CH_3) has a measured relative intensity of 30.4%; the base peak had a *m/e* of 176. In contrast, compound IVa (R = CH_3) gave a more stable molecular ion with relative intensity of 81.3%.

Treatment of IVa (R = CH_3) with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, Vitride) in refluxing benzene gave the amine I (R = CH_3; R′ = H; R″ = H), isolated as the hydrochloride salt, in 89% yield. The pentamethoxy I (R = CH_3; R′ = H; R″ = OCH_3) was prepared in a similar manner from IIb and trimethoxycinnamoyl chloride.

The *N*-acetyl amine derivative, I (R = CH_3; R′ = $COCH_3$; R″ = H), which was prepared from I (R = CH_3; R′ = H; R″ = H) with a mixture of acetic anhydride and pyridine in 78% yield, was also reduced with Red-Al in refluxing benzene to furnish 7,8-dimethoxy-2-ethyl-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]-isoindoline (I, R = CH_3; R′ = C_2H_5; R″ = H).

Experimental Section

All melting points were taken on a Thomas–Hoover melting point apparatus. The pmr spectra were determined on Varian A-60 and Varian HA-100 D spectrometers. The mass spectra data were obtained with a Varian Mat CH-4B mass spectrometer. Infrared spectra were taken on a Perkin-Elmer 337 Infracord. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer.

2-Bromo-4,5-dimethoxyphenylpropionitrile.—A solution of 100 g of 3,4-dimethoxycinnamonitrile (mixture of cis and trans, Aldrich) in 450 ml of tetrahydrofuran was hydrogenated under 2.8 kg/cm^2 of H_2 for 48 hr with 1.5 g of 5% Pd/C. Filtration of the reaction mixture and removal of solvent yielded 96 g of syrupy 3,4-dimethoxyphenylpropionitrile. This was dissolved in 300 ml of acetic acid. The solution was cooled to 18° and to it was slowly added, with stirring, a solution of 85 g of Br_2 in 50 ml of acetic acid over 1 hr. The mixture was stirred for an additional 1.5 hr, then poured onto a mixture of 51 g of potassium acetate, 250 ml of water, and 300 g of ice. Crude 2-bromo-4,5-dimethoxyphenylpropionitrile separated as crystals. Recrystallization twice from methanol–water gave 63.2 g (48% yield) of product, mp 76–78°. An analytical sample was prepared by an additional recrystallization from methanol, mp 75–76°, ir (Nujol) ν_{max} 2230 cm^{-1} (C≡N, w).

Anal. Calcd for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 49.17; H, 4.50; N, 5.28.

1-Cyano-4,5-dimethoxybenzocyclobutene (IIa, R = CH_3).—A 5-l. three-necked flask equipped as reported by Bunnett and Skorez[5] was flame-dried and flushed with dry helium. The flask was half-filled with anhydrous liquid ammonia; then small pieces (<50 mg) of potassium were added until the intense blue color of the solution persisted for several minutes. A small crystal of ferric nitrate was added followed by portionwise addition of freshly cut potassium (18.7 g). After the color of the blue solution changed to dull brown, 32.3 g of 3-(2-bromo-4,5-dimethoxy)phenylpropionitrile was rapidly added in one portion. The reaction mixture was stirred for 6 min and 41 g of ammonium nitrate was added to neutralize the basic mixture. Ammonia was allowed to evaporate and the residue was treated with a mixture of 150 ml of $CHCl_3$ and 150 ml of H_2O. The aqueous portion was extracted three times with $CHCl_3$ (500 ml) and the combined $CHCl_3$ solution was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was concentrated to a viscous oil and eluted with chloroform through a 50-mm (i.d.) column containing acid-washed alumina (300 g, Fisher, Brockman activity I). The product was isolated as a white powder from the initially eluted component. It was triturated with hexane to give 16.8 g (74.4% yield) of IIa, mp 83–84°. An analytical sample was obtained by recrystallization from ethanol, mp 83–84°, ir (Nujol) ν_{max} 2220 cm^{-1} (C≡N).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.78; H, 5.55; N, 7.27.

1-Aminomethyl-4,5-dimethoxybenzocyclobutene Hydrochloride (IIb, R = CH_3).—A solution of 27 g of IIa in 150 ml of 1 *M* BH_3 in tetrahydrofuran was stirred under helium at room temperature for 3 hr. Absolute EtOH (19 ml) was then cautiously added. After 15 min, 39 g of 21% ethanolic HCl was added and the resulting suspension was stirred overnight. The desired product was isolated as a white powder (28 g, 85% yield), mp 196–198°. An analytical sample was prepared by recrystallization from 2-propanol, mp 201–203°, ir (Nujol) ν_{max} 3125 and 2575 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}NO_2 \cdot HCl$: C, 57.52; H, 7.02; N, 6.10. Found: C, 57.78; H, 7.15; N, 5.92.

***N*-[(4,5-Dimethoxybenzocyclobuten-1-yl)methyl]cinnamamide (IIIa, R = CH_3).**—A mixture of 4.05 g of IIb and 3.30 g of cinnamoyl chloride in 18 ml of dry pyridine was heated on a steam bath for 1 hr. The resulting solution was allowed to stand at room temperature for 2 hr and poured, with stirring, into a mixture of ice and water (200 ml) and left overnight. The resulting solid product was collected by filtration, washed with water, and recrystallized from EtOH–H_2O to give 5.23 g (92% yield) of off-white solid, mp 133–134°. Recrystallization from ethyl acetate gave analytically pure IIIa (R = CH_3) as white needles: mp 138–138.5°; ir (Nujol) ν_{max} 3320, 3275, 1650, 1620, 1320 cm^{-1}; mass spectrum *m/e* 324 (M^+ + 1, 6.2%), 323 (M^+, 30.4%), 177 (46.8%), 176 (100%), 163 (46.8%).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.27; H, 6.55; N, 4.33. Found: C, 74.31; H, 6.64; N, 4.23.

***N*-[(4,5-Dimethoxybenzocyclobuten-1-yl)methyl]-3,4,5-trimethoxycinnamamide (IIIb, R = CH_3).**—This compound was prepared in a similar manner from 4.41 g of IIb, 5.60 g of 3,4,5-trimethoxycinnamoyl chloride and 25 ml of pyridine. Recrystallization from a mixture of EtOH and H_2O gave 5.83 g of product, mp 152–153°. An analytical sample was prepared by recrystallization from ethyl acetate: mp 152–153°; ir (Nujol) ν_{max} 3370, 1675, 1640, 1575 cm^{-1}; uv (EtOH) λ_{max} 230 nm (log ε 4.48), 295 (4.43); mass spectrum *m/e* 413 (M^+).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 67.05; H, 6.88; N, 3.48.

7,8-Dimethoxy-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]isoindolin-3-one (IVa, R = CH_3).—A solution of 15.0 g of IIIa (R = CH_3) in 730 ml of toluene was heated at 195–200° for 47 hr. The product, which separated from the cooled reaction

(3) I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970).

(4) $LiAlH_4$ or Raney nickel reduction of an analogous nitrile to the corresponding amine was reported. *Cf.* Belgian Patent 635,901 (1964); *Chem. Abstr.*, **62**, 3987 (1965).

(5) J. F. Bunnett and J. A. Skorez, *J. Org. Chem.*, **27**, 3836 (1962).

mixture, was collected by filtration and washed with ether to give 9.5 g (63% yield) of a light yellow solid, mp 244–246°. Recrystallization from $CHCl_3$–MeOH yielded 8.5 g of analytically pure white crystals: mp 249–250°; ir (Nujol) 3190 (NH), 1695 cm^{-1} (C=O, γ-lactam); uv (EtOH) λ_{max} 230 nm (log ε 4.00), 285 (3.76); nmr ($CDCl_3$–TMS) δ 7.24 (5 P, s, Ar H), 6.66 (1 P, s, Ar H), 6.52 (1 P, s, Ar H), 6.11 (1 P, NH), 3.86 (3 P, s, Ar OCH_3), 3.82 (3 P, s, Ar OCH_3), 3.80–2.00 (7 P, m, methine and methylene hydrogens); mass spectrum *m/e* 324 (M^+ + 1, 20.3%), 323 (M^+, 81.3%), 279 (24.2%), 266 (20.3%), 232 (46.0%), 193 (34.0%), 192 (24.2%), 189 (25.0%), 176 (34.4%), 161 (40.5%), 131 (81.3%).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.36; H, 6.34; N, 4.42.

7,8-Dimethoxy-4-(3,4,5-trimethoxyphenyl)-3a,4,5,9b-tetrahydrobenz[*e*]isoindolin-3-one (IVb, R = CH_3).—A solution of 4.25 g of IIIb in 250 ml of toluene was heated at 210–225° for 48 hr. The product was collected in a similar manner as described for IVa (R = CH_3) and dried at 120° *in vacuo* to give 2.19 g of white crystals, mp 223–225°. An analytical sample was prepared by recrystallization from toluene: mp 225–227°; ir (Nujol) 3220, 1695, 1590, 1130 cm^{-1}; uv (EtOH) λ_{max} 282 nm (log ε 3.83); mass spectrum *m/e* 413 (M^+).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.79; H, 6.45; N, 3.31.

7,8-Dimethoxy-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]isoindoline Hydrochloride (I HCl, R = CH_3; R′ = H; R″ = H).—A boiling solution of 8.1 g of IVa (R = CH_3) in 350 ml of dry benzene was rapidly cooled and the resulting fine suspension was treated with 25 ml of Red-Al. The mixture was refluxed for 2.5 hr, cooled, and to it was cautiously added 200 g of 10% aqueous NaOH. The separated aqueous layer was extracted with 100 ml of benzene. The combined benzene extracts were washed with saturated aqueous NaCl solution, filtered, and distilled to remove most of the benzene. Anhydrous Et_2O (100 ml) was added. The mixture was stirred in an ice bath while 8 g of 21% ethanolic HCl in 100 ml of anhydrous Et_2O was added dropwise. The solid was collected by filtration, washed with Et_2O and dried to give 7.7 g (89% yield) of white powder. An analytical sample was obtained by precipitation from a methanolic solution with Et_2O: mp 285° dec; ir (Nujol) ν_{max} 2700, 2400 cm^{-1}; nmr ($CDCl_3$–TMS) δ 7.24 (5 P, s, Ar H), 6.62 (1 P, s, Ar H), 6.46 (1 P, s, Ar H), 3.83 (6 P, s, Ar OCH_3), 3.80–2.00 (9 P, m).

Anal. Calcd for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.28; H, 7.06; N, 3.83.

7,8-Dimethoxy-4-(3,4,5-trimethoxyphenyl)-3a,4,5,9b-tetrahydrobenz[*e*]isoindoline Hydrochloride (I HCl, R = CH_3; R′ = H; R″ = OCH_3).—This compound was prepared in a similar manner from 2.06 g of IVb and 170 ml of benzene. The product, 2.02 g (93% yield), was collected as a white powder, mp 261–262°. An analytical sample was prepared by precipitation from a methanolic solution with Et_2O: mp 261–262°; ir (Nujol) 3400, 2700, 2400, 1590, 1130 cm^{-1}; uv (EtOH) λ_{max} 282 nm (log ε 3.66); mass spectrum *m/e* 399 (M^+ − HCl).

Anal. Calcd for $C_{23}H_{29}NO_5 \cdot HCl$: C, 63.37; H, 6.94; N, 3.21. Found: C, 63.49; H, 7.05; N, 3.14.

2-Acetyl-7,8-dimethoxy-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]-isoindoline (I, R = CH_3; R′ = $COCH_3$; R″ = H).—A mixture of 2.28 of I HCl (R = CH_3; R′ = H, R″ = H), 10 ml of Ac_2O, and 10 ml of pyridine was stirred at room temperature for 16 hr. After the usual work-up the residue was recrystallized from a mixture of EtOAc and heptane to give 1.8 g (78% yield) of product, mp 178–180°. An additional recrystallization from EtOAc yielded an analytically pure sample: mp 181–182°; ir (Nujol) ν_{max} 1630 cm^{-1} (C=O); mass spectrum *m/e* 352 (M^+ + 1, 24.9%), 351 (M^+, 100%), 292 (10.2%), 279 (55.0%), 265 (20.0%).

Anal. Calcd for $C_{22}H_{25}NO_3 \cdot {}^1/_4H_2O$: C, 74.23; H, 7.22; N, 3.94. Found: C, 74.40; H, 7.40; N, 3.96.

7,8-Dimethoxy-2-ethyl-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]-isoindoline Hydrochloride (I HCl; R = CH_3; R′ = C_2H_5; R″ = H).—To a solution of 1.70 g of the aforementioned acetamide in 100 ml of dry benzene was added 4 ml of Red-Al. The mixture was refluxed for 1 hr and cooled. To the mixture was cautiously added, with stirring, 100 ml of 10% aqueous NaOH solution. The benzene layer was separated, washed with 100 ml of saturated aqueous NaCl solution, dried (Na_2SO_4), and filtered. The filtrate was evaporated *in vacuo* and the residual syrup diluted with 200 ml of anhydrous Et_2O. To this was added 5 ml of 20% ethanolic HCl and the precipitated white powder was collected by filtration to give 1.69 g (94% yield) of product, mp 278–280°. An analytically pure sample was prepared by dissolving the product in methanol and reprecipitation with ether, mp 279–280°, ir (Nujol) ν_{max} 2440 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}NO_2 \cdot HCl$: C, 70.66; H, 7.55; N, 3.75. Found: C, 70.63; H, 7.62; N, 3.59.

Registry No.—I (R = CH_3; R′ = $COCH_3$; R″ = H), 35202-50-7; I HCl (R = CH_3; R′ = H; R″ = H), 35202-51-8; I HCl (R = CH_3; R′ = H; R″ = OCH_3), 35202-52-9; I HCl (R = CH_3; R′ = C_2H_5; R″ = H), 35202-53-0; IIa (R = CH_3), 35202-54-1; IIb (R = CH_3), 35202-55-2; IIIa (R = CH_3), 35202-56-3; IIIb (R = CH_3), 35202-57-4; IVa (R = CH_3), 35202-58-5; IVb (R = CH_3), 35202-59-6; 2-bromo-4,5-dimethoxyphenypropionitrile, 35249-62-8.

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Syntheses of the Dihydronepetalactones

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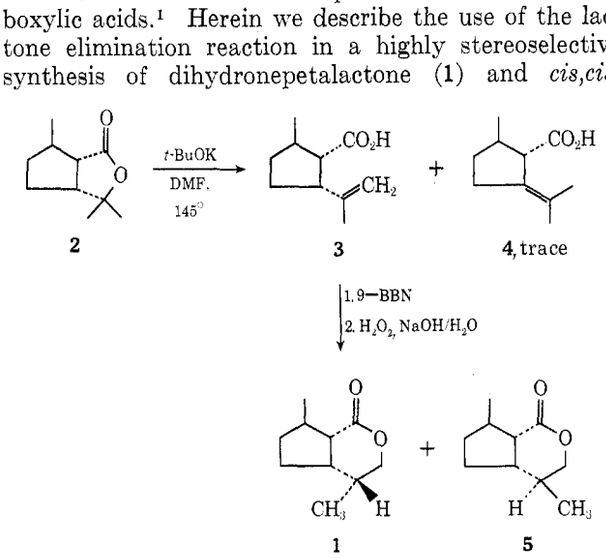
During a study of the base-catalyzed cyclization of methyl 6,7-epoxycitronellate it was discovered that alkoxides act on lactones to produce unsaturated carboxylic acids.[1] Herein we describe the use of the lactone elimination reaction in a highly stereoselective synthesis of dihydronepetalactone (**1**) and *cis,cis*-



dihydronepetalactone (**10**). Dihydronepetalactone (**1**), the enantiomer of a major constituent of matatabi-

(1) J. Wolinsky, P. Hull, and E. J. Eustace, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., spring, 1971. Details of this work will be described in a forthcoming publication.