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(31) Reference 27, p 102.
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Cyclobutene Derivatives as Isoprene Equivalents in Terpene Synthesis. 3. Bicyclo[2.2.0]hexanes[1]

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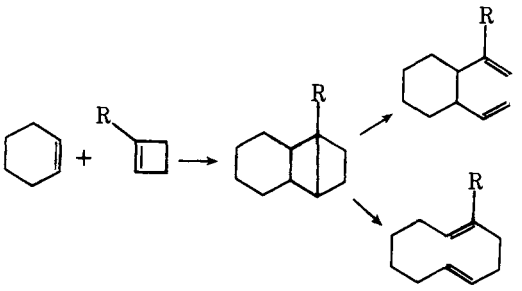
Abstract: Two new syntheses of cyclobutene esters and the use of 1-cyanocyclobutene as potential isoprene synthons are described. Photocycloaddition of methyl cyclobut-1-enecarboxylate and 1-cyanocyclobutene to piperitone, followed by reduction and lactonization, gives photodihydroaristolactone **15**. Single-crystal X-ray analysis of **15** and related **4** reveals interesting structural features in the strained bicyclo[2.2.0]hexane system. Thermolysis of lactones **15** and **4** yields 1,5-cyclodecadienes related to germacrene sesquiterpenes.

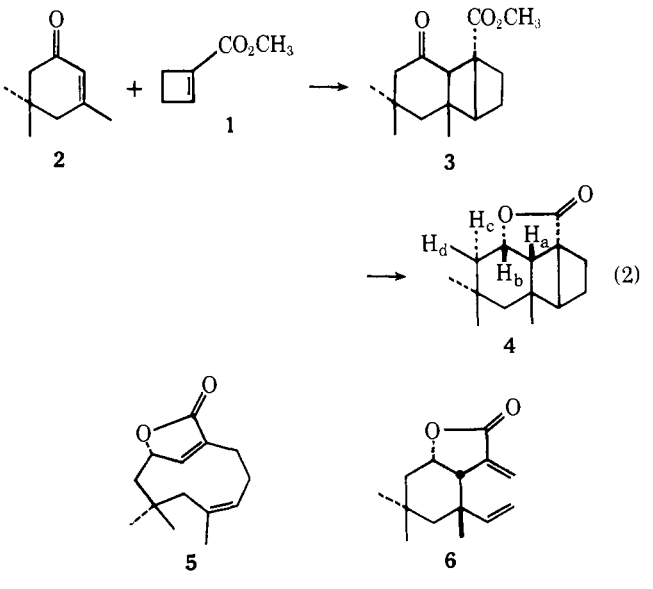
As part of a continuing program of terpene synthesis, we have for several years been attempting to utilize cyclobutenes as reactive isoprene synthons.[2a,b] Ring opening of suitable cyclobutenes may be induced to occur in either of two directions yielding "terminal"[2a,2c] or "internal"[2b] isoprene residues. Cycloaddition reactions of cyclobutene derivatives (eq 1) leads



(1)

to strained bicyclo[2.2.0]hexanes capable of thermolysis to either 1,5-cyclodecadienes or divinylcyclohexanes. The photocycloaddition of cyclobutenes is the best route to strained bicyclo[2.2.0]hexane derivatives,[3] and ample evidence has accumulated that the cycloreversion of bicyclo[2.2.0]hexanes proceeds with some stereospecificity.[4]

The importance of medium-ring carbocycles such as germacradienes[5] has prompted a number of recent elegant approaches to these molecules[6] including several using the strategy outlined in eq 1.[7] For example, photocycloaddition[7b] of methyl cyclobutenecarboxylate (**1**) and isophorone (**2**) (eq 2) gave derivative **3** which was converted to lactone **4**. Lactone **4** can by pyrolyzed at 185 °C yielding **5** and **6**. Since germacrene-type sesquiterpenes undergo Cope rearrangement to



(2)

elemanes,[8] the bicyclo[2.2.0]hexane approach possesses general features which are attractive in terpene syntheses. We report herein our efforts in this area.[9]

Synthesis of Cyclobutene Derivatives. It was clear from the outset that, for a cyclobutene-based methodology to be generally applicable, efficient routes to the reactive precursors must be available. In our experience the lengthy[12] synthesis of **1** gave low overall yields. Consequently, two new routes to cyclobutene esters were developed (eq 3 and 4). Both sulfen-

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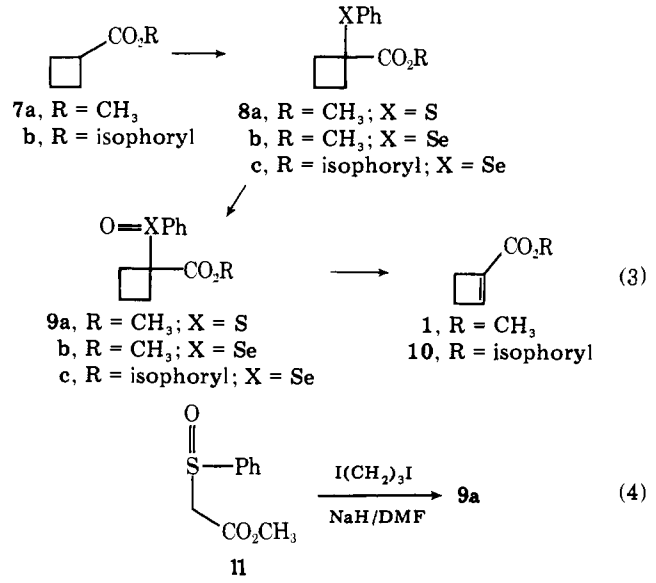
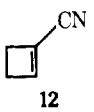


ylation-dehydrosulfenylation and selenenylation-dehydroselenenylation are applicable to the synthesis of cyclobut-1-enecarboxylates.[13] The more volatile **1** is best prepared via the sulfoxide, whereas ester **10** is most conveniently available via the selenoxide route. The relatively sensitive cyclobutene ester **1** was generated as needed by pyrolysis of sulfoxide **9a** (160 °C, 57% yield).

A second route to **9a** which also *forms* the cyclobutane ring was explored. Cyclialkylation of methyl 1-phenylsulfinoacetate (**11**) with 1,3-diiodopropane in DMF containing **2** equiv of sodium hydride gave **9a** (in 39% yield). We have also investigated some chemistry of 1-cyanocyclobutene (**12**), a more



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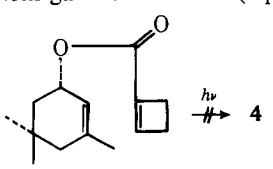
readily accessible isoprene synthon obtained by dehydrocyanation of the acrylonitrile dimer 1,2-dicyanocyclobutene in yields around 60%.[14] The ready accessibility of this reactive cyclobutene makes 1-cyanocyclobutene (**12**) an **inexpensive**[12c] and attractive alternative to ester **1**.

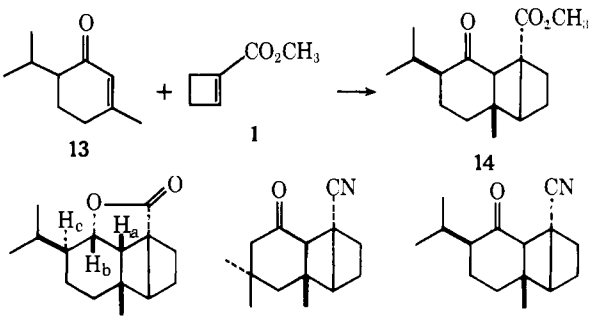
Attempted Intramolecular Cycloaddition. With various cyclobutenes in hand, their photocycloadditions was investigated. The *intramolecular* [2 + 2] cycloaddition[15] of ester **10** under a variety of conditions gave little or no **4** (eq 5). The reaction



10

is characterized by slow disappearance of the cyclobutene NMR signal and the unsaturated carbonyl in the IR and the appearance of saturated carbonyl due to the photodimer of **10**. Inspection of molecular models indicates that the cyclobutene π system is not correctly oriented with respect to the double bond and in addition suffers nonbonded interactions with the vinylic methyl group.

The Intermolecular Route. Following Wender's[7b] method, photocycloaddition of **1** to piperitone (**13**) yields the adduct **14** (49%). This compound was characterized by carbonyl absorptions at 5.83 (ester) and 5.93 μ (ketone) as well as NMR signals at δ 3.64 (3 H, s, methyl ester) and 1.23 (3 H, s, angular methyl group). Reduction of **14** followed by lactonization yields **15** (mp 60–61.5 °C). In addition, photolysis of 1-cyanocyclobutene (**12**) and either isophorone (**1**) or piperitone

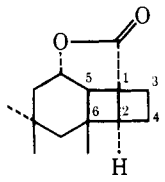


(**13**) yield adduct **16** (38%) and **17** (48%), respectively. Compound **16** possessed bands at 1715 (ketone) and 2257 cm^{-1} (nitrile) and NMR signals for methyl groups at δ 1.3, 1.1, and 0.98. Compound **17** shows bands at 1709 (ketone) and 2242 cm^{-1} (nitrile) and three methyls at δ 1.2, 0.98 (d, J = 7 Hz), and 0.95 (dd, J = 7 Hz). Both **16** and **17** were converted to the corresponding lactones **4** and **5** ($NaBH_4$; H^+). Comparison of the methine hydrogen (C-6) of **4** (δ 4.8, dt, J = 5, 10 Hz) with that of lactone **15** (δ 4.7, d, J = 10 Hz) allows us to assign a β configuration to the isopropyl group as shown.[16] Inspection of molecular models of **15** indicates that the H_b–H_c dihedral angle can closely approximate 90° and thus give a coupling constant close to 0 Hz. The assignment and the structures of lactone **4** and **15** were additionally confirmed by single-crystal X-ray diffraction experiments (Figures 1[17] and 2). The NMR analysis is confirmed by the observed dihedral angles (Table I).[17] The dihedral angle H_a–H_b is 1° in **4** and 8° in **15**. The slight increase in angle is reflected in a decrease (9.5 to 9.0 Hz) in J_{ab}. The angle H_b–H_c, however, increases from 60 to 72°. The >70° dihedral angle means that J_{bc} is effectively zero. This increase in the H_b–H_c angle is due to the half-chair cyclohexane ring being slightly skewed in Wender's[7b] lactone **4** because of a nonbonded interaction between a pseudoaxial (C_{13}) methyl group and the bicyclo[2.2.0]hexane bridgehead carbon (C_1). This skew is also reflected in the C_6–C_7/C_8–C_9 dihedral angle of 50° for **4** vs. 60° for **15** and in the "best molecular fit" of **4** and **5** (vide infra). The configuration of the isopropyl group is that expected for [2 + 2] cycloaddition to the less hindered side of **15** (opposite from the isopropyl) which yields materials with the usual terpene configuration.

Bicyclo[2.2.0]hexanes. The structure of the bicyclo[2.2.0]-hexane portion of **4** and **15** is now considered. Of the number of cyclobutane structures that have been studied,[18a,b] two distinctive features are apparent: (1) the generally longer bond lengths of cyclobutanes[19] and (2) a "puckered" conformation. The average bond length of 119 separate determinations[18a] is 1.55 Å. The dihedral angle β between the two planes in puckered cyclobutane varies from 0 to 35°. A recent careful study[20] of cyclobutane shows that the parent hydrocarbon is puckered 26 ± 3°.

Using a substructure search of the Cambridge Crystallographic Data File,[21] we have obtained coordinates for three[22] additional bicyclo[2.2.0]hexanes (**19, 20,** and **21**), besides **4** and **15**. For comparison purposes we have also used the parent hydrocarbon **18,** whose structure was solved by electron diffraction.[23,24] All pertinent C–C bond distances in bicyclo[2.2.0]hexanes **4, 15,** and **18–21** are collected in Table II.[17] Of particular note is the extremely long C_1–C_2 bond (average 1.575 Å). This long bond is undoubtedly the weakest bond and indeed is the bond which cleaves in the subsequent thermolysis reaction.[25]

The puckering of the two fused cyclobutane rings is largely suppressed, owing to the constraints of the cis ring fusion. These angles, calculated for each cyclobutane, are collected in Table III.[17] When an addition ring is fused as in **4, 15,** or **19** the cyclobutane rings are virtually flat. In **18** and **20** the



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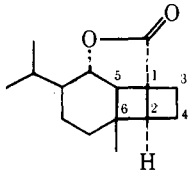

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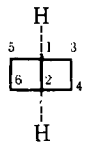

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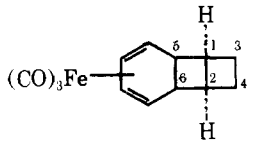

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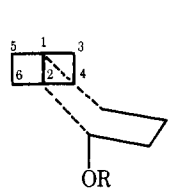

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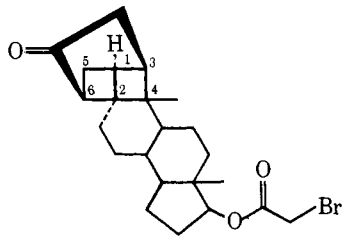

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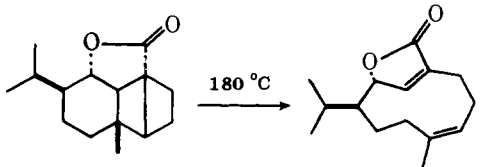
puckering is modest (11.5–14.2°) and in **21** is *very large* owing to the two-carbon bridge connecting C_3 and C_6.

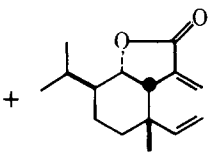
The molecular similarity of the set of six bicyclo[2.2.0]-hexanes is best seen by a least-squares fitting procedure we have used previously.[26] The "best molecular fit" program[27,28] was used to compare the geometries of C_1–C_6 and the results are shown in Table IV.[17]

As expected lactones **4** and **15** are very similar. Not shown are the Δ's for C_7 and C_8, 0.13 and 0.26, respectively, which again points to the difference in skew in the cyclohexane rings of **4** and **15**. The fits of **18–21** are consistent with the previously discussed differences in puckering. This is particularly apparent in the opposite "corners" C_4 and C_5 of **18** and **20**.

Completion of the Synthesis. The conversion of **15** into terpenoid **22** was achieved by thermolysis. Only a modest amount (22%) of the corresponding elemane-like **23** was formed. Compound **22** is a *Z* isomer related to dihydroaristolactone (**24**).[29] Compound **23** possesses spectral properties consistent



15 **22**



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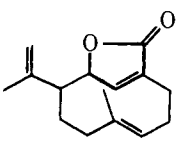

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with conformer A, in particular, very low-field absorption of H_5 (δ 7.19 in $CDCl_3$ or 7.02 in CCl_4) as a result of the anisotropic shielding of the 1(10) double bond.[8,30]

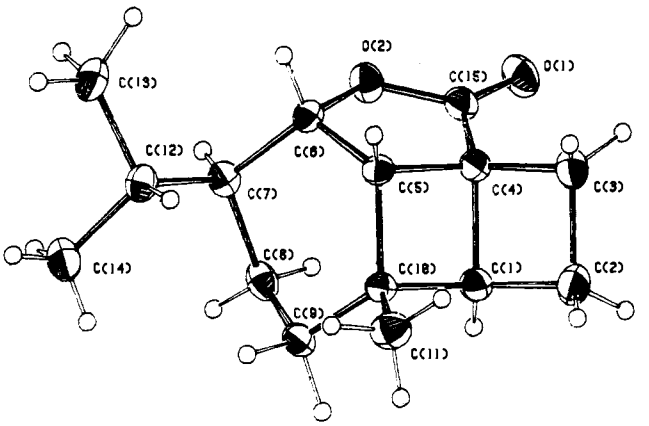
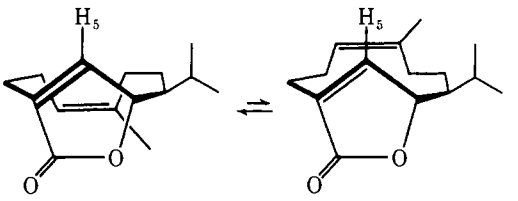


Figure 2. ORTEP drawing of **15**.



A B

Thus, the bicyclo[2.2.0]hexane route is proven to be a viable approach[7] to the germacrene skeleton. Further applications of unique isoprene synthons are currently being investigated.

Experimental Section

Melting points were measured in capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on Varian HR-220, T-60A, and EM-360 spectrometers. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Mass spectra (70 eV) were obtained on Varian MAT CH-7 and AEI MS-9 spectrometers. IR spectra were obtained in solution cells with chloroform or on neat samples using a Perkin-Elmer 137 Infracord. Analytical gas chromatography was performed with a Varian Aerograph Model 940 with FID detector on a 1.5% OV-101 on Chromosorb G column (5 ft × 1/8 in.) with helium carrier gas. Distillations were performed with a Büchi/Brinkmann Standard Micro distillation oven, Model KR, and boiling points reported are approximate. Both ether and tetrahydrofuran were dried by distillation from lithium aluminum hydride. All experiments were routinely done under an inert atmosphere.

Methyl 1-Cyclobutane-1-phenylthiocarboxylate (8a). To a stirred solution of lithium diisopropylamide (30 mL of THF, 1.4 mL of diisopropylamine, and 6.3 mL of a 1.6 M *n*-butyllithium solution, at −78 °C) was added dropwise a solution of 1 g (8.8 mmol) of methyl cyclobutanecarboxylate (**7a**) in 10 mL of THF. This was stirred for 15 min, and 2 g of diphenyl disulfide in 10 mL of THF was added in one portion. The resulting mixture was stirred for 15 min. The cold reaction mixture was poured into 10% HCl and extracted into a 50/50 ether–pentane mixture. The organic layer was washed successively with water, sodium bicarbonate solution, and brine, dried over sodium sulfate, and concentrated under reduced pressure. Column chromatography (5/95 ether–pentane) gave 1.5 g (77%) of methyl 1-cyclobutane-1-phenylthiocarboxylate (**8a**): IR (film) 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (5 H, m), 3.64 (3 H, s), 1.8–2.9 (6 H, m); mass spectrum *m/e* (% base) 222 (14), 135 (80), 83 (32), 55 (100). Calcd for $C_{12}H_{14}O_2S$: mol wt, 222.0715. Found: mol wt, 222.0703.

Methyl 1-Cyclobutane-1-phenylselenocarboxylate (8b). To a stirred solution of lithium diisopropylamide (15 mL of THF, 0.7 mL of diisopropylamine, and 3.2 mL of a 1.6 M *n*-butyllithium solution, at −78 °C) was added dropwise a solution of 500 mg of methyl cyclobutanecarboxylate (**8a**) in 5 mL of THF. This was stirred for 15 min, and 1.43 g of diphenyl diselenide in 5 mL of THF was added in one portion. The resulting mixture was stirred for 15 min. The cold reaction mixture was poured into 10% HCl and extracted into a 50/50 ether–pentane mixture. The organic layer was washed successively

with water, sodium bicarbonate solution, and brine, dried over sodium sulfate, and concentrated under reduced pressure. Preparative TLC (2/98 ether–pentane) gave 661 mg (56%) of methyl 1-cyclobutane-1-phenylselenocarboxylate (**8b**): IR ($CHCl_3$) 1718 cm^{-1}; NMR ($CDCl_3$) δ 7.50 (5 H, m), 3.68 (3 H, s), 1.6–3.1 (6 H, m); mass spectrum *m/e* (% base) 270 (28), 113 (75), 81 (58), 77 (54), 59 (93), 55 (59), 53 (100). Calcd for $C_{12}H_{14}O_2Se$: mol wt, 270.0160. Found: mol wt, 270.0171.

Methyl 1-Phenylsulfinoacetate (11). Thiophenol (11.55 g, 105 mmol) was added with stirring to a solution of 4.2 g of sodium hydroxide in 200 mL of methanol and stirred for 0.5 h. Methyl chloroacetate (10.9 g, 100 mmol) was added dropwise and the resulting solution was stirred for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water and extracted into ether. The organic layer was washed with a 5% sodium hydride solution and dried over sodium sulfate. Distillation gave 15.5 g (85%) of methyl 1-phenylthioacetate: bp 93–95 °C (0.6 mm); IR (film) 1724 cm^{-1}; NMR ($CDCl_3$) δ 7.32 (5 H, m), 3.66 (3 H, s), 3.63 (2 H, s); mass spectrum *m/e* (% base) 182 (56), 125 (8), 124 (6), 123 (100), 109 (12), 77 (12), 65 (10), 51 (13). Calcd for $C_9H_{10}O_2S$: mol wt, 182.0402. Found: mol wt, 182.0404.

Methyl 1-phenylthioacetate (9.1 g, 50 mmol) was dissolved in 60 mL of water and 30 mL of methanol and stirred for 12 h at room temperature in the presence of 11.28 g (55 mmol) of sodium metaperiodate. The reaction mixture was filtered and the product was extracted into dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Distillation gave 9.35 g (94%) of methyl 1-phenylsulfinoacetate (**11**): bp 130–131 °C (0.5 mm); mp (pentane) 47–49 °C; IR ($CDCl_3$) 1734 cm^{-1}; NMR ($CDCl_3$) δ 7.6 (5 H, m), 3.80 (2 H, m), 3.70 (3 H, s); mass spectrum *m/e* (% base) 198 (26), 126 (7), 125 (100), 123 (9), 97 (17), 77 (32), 65 (5), 51 (17). Calcd for $C_9H_{10}O_3S$: mol wt, 198.0351. Found: mol wt, 198.0338.

Isophoryl Cyclobutanecarboxylate (7b). A solution of 8.4 g of isophorol and 45 g of pyridine was stirred at 0 °C while 11 g of cyclobutanecarboxylic anhydride was added dropwise. The resulting solution was allowed to warm to room temperature and was stirred for 4 days. The mixture was then cooled, poured into 300 mL of dilute hydrochloric acid, and extracted into three 150-mL portions of methylene chloride. The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate, and concentrated under reduced pressure. Distillation of the residue gave 10.7 g (80%) of isophoryl cyclobutanecarboxylate (**7b**): bp 85–89 °C (0.4 mm); IR (film) 1715 cm^{-1}; NMR ($CDCl_3$) δ 5.47 (2 H, m), 2.8–3.5 (1 H, m), 1.72 (3 H, s), 1.00 (3 H, s), 0.96 (3 H, s), 0.8–2.8 (10 H, m); mass spectrum *m/e* (% base) 222 (5), 123 (47), 122 (34), 107 (100), 91 (19), 83 (44), 81 (19), 55 (87). Calcd for $C_{14}H_{22}O_2$: mol wt, 222.1621. Found: mol wt, 222.1616.

Isophoryl 1-Cyclobutane-1-phenylselenocarboxylate (8c). To a stirred solution of lithium diisopropylamide (10 mL of THF, 0.46 mL of diisopropylamine, and 1.25 mL of a 2.4 M *n*-butyllithium solution, at −100 °C) was added dropwise a solution of 555 mg of isophoryl cyclobutanecarboxylate (**7b**) in 2 mL of THF. The resulting solution was stirred for 15 min, 940 mg of diphenyl diselenide in 2 mL of THF was added in one portion, and the mixture was stirred for 5 min. The cold reaction mixture was poured into 50 mL of dilute hydrochloric acid and extracted into a 20/80 ether–pentane mixture. The organic layer was washed with water, sodium bicarbonate solution, and brine, dried over sodium sulfate, and concentrated under reduced pressure. Preparative thin layer chromatography (5/95 ether–pentane) gave 616 mg (65%) of isophoryl 1-cyclobutane-1-phenylselenocarboxylate (**8c**): IR ($CHCl_3$) 1706 cm^{-1}; NMR ($CDCl_3$) δ 7.45–7.80 (2 H, m), 7.2–7.45 (3 H, m), 5.25 (2 H, m), 1.65 (3 H, s), 0.90 (3 H, s), 0.86 (3 H, s), 0.8–2.9 (10 H, m); mass spectrum *m/e* (% base) 378 (2), 211 (32), 130 (36), 123 (100), 122 (49), 107 (41), 81 (35), 53 (33). Calcd for $C_{20}H_{26}O_2Se$: mol wt, 378.1099. Found: mol wt, 378.1095.

Methyl 1-Cyclobutane-1-phenylsulfinocarboxylate (9a). Method A. The sulfide (1.5 g) **8a** was dissolved in 15 mL of water and 5 mL of methanol. The mixture was stirred for 3 days at room temperature in the presence of 1.98 g of sodium metaperiodate. The reaction mixture was filtered and the solid material was washed with methylene chloride. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give 1.2 g (75%) of sulfoxide **9a**, mp 60–62 °C (pentane).

Method B. Dry sodium hydride (240 mg) was suspended in dimethylformamide and stirred while 1.0 g of methyl 1-phenylsulfinoacetate in 10 mL of dimethylformamide was added dropwise. The mixture was stirred for 1 h following the addition. 1,3-Diiodopropane (1.48 g) was added in small portions and the resulting mixture was stirred overnight. The reaction mixture was poured into 100 mL of water and extracted into chloroform. The organic layer was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. Preparative TLC (90/10 diethyl ether–pentane) gave 469 mg (39%) of methyl 1-cyclobutane-1-phenylsulfinocarboxylate: mp (pentane) 59–61 °C; IR ($CHCl_3$) 1724, 1042 cm^{-1}; NMR ($CDCl_3$) δ 7.52 (5 H, m), 3.68 (3 H, s), 1.7–3.2 (6 H, m); mass spectrum *m/e* (% base) 238 (1), 113 (100), 81 (53), 78 (13), 78 (13), 77 (14), 59 (36), 55 (12), 53 (27), 51 (10). Calcd for $C_{12}H_{14}O_3S$: mol wt, 238.0664. Found: mol wt, 238.0676.

Methyl Cyclobut-1-enecarboxylate (1). Method A. The sulfoxide (90 mg) **9a** was heated to 160 °C in a bulb-to-bulb distillation apparatus. The unsaturated ester **1** was collected by distillation over a 45-min period, yielding 24 mg (57%).

Method B. Methyl 1-cyclobutane-1-phenylselenocarboxylate (194 mg) (**9b**) was stirred at room temperature under nitrogen in 3 mL of dichloromethane in the presence of 100 mg of pyridine, 1 mL of a 30% solution of H_2O_2, and 1 mL of water. The reaction mixture was stirred for 4 h. The reaction mixture was poured into 100 mL of water and extracted into dichloromethane. The organic layer was washed with a sodium bicarbonate solution, followed by dilute HCl, and distillation yielding 26 mg (32%) of compound **1**: λ_{max} (hexane) 221 nm (ϵ 2400); IR ($CHCl_3$) 1705, 1600 cm^{-1}; NMR ($CDCl_3$) δ 6.80 (1 H, s), 3.74 (3 H, s), 2.75 (2 H, m), 2.52 (2 H, m); mass spectrum *m/e* (% base) 112 (33), 81 (35), 59 (12), 53 (100), 50 (10), 43 (93). Calcd for $C_6H_8O_2$: mol wt, 112.0525. Found: mol wt, 112.0526.

Isophoryl Cyclobut-1-enecarboxylate (10). Isophoryl 1-cyclobutane-1-phenylselenocarboxylate (100 mg) (**9c**) was stirred overnight at room temperature under argon in 0.75 mL of water and 4.5 mL of methanol in the presence of 50 mg of sodium bicarbonate and 11 mg of sodium metaperiodate. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted into a 10/80 ether–pentane mixture. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. Preparative thin layer chromatography (5/95 ether–pentane) followed by bulb-to-bulb distillation gave 40 mg (69%) of isophoryl cyclobut-1-enecarboxylate (**10**): bp 90–100 °C (0.5 mm); IR ($CHCl_3$) 1689, 1686 cm^{-1}; NMR ($CDCl_3$) δ 6.72 (1 H, broad s), 5.35 (2 H, m), 2.68 (2 H, m), 2.44 (2 H, m), 1.67 (3 H, s), 0.96 (3 H, s), 0.91 (3, H, s), 0.80–2.50 (4 H, m); mass spectrum *m/e* (% base) 220 (2), 123 (21), 122 (27), 107 (100), 91 (24), 81 (41), 79 (18), 53 (26). Calcd for $C_{14}H_{20}O_2$: mol wt, 220.1464. Found: mol wt, 220.1451.

1-Cyanocyclobutene (12) was prepared by a modification of the method of Gale.[14] A 2.5 × 40 cm vertical quartz tube packed with 8–20 or 20–30 mesh Ascarite was heated to 200–220 °C in a flow of nitrogen. After 2 h a stoppered dropping funnel containing 6 g (57 mmol) of 1,2-dicyanocyclobutane (Aldrich) was placed on top of the tube and a trap cooled in dry ice–acetone at the bottom. The system was evacuated to 1–2 mm and 1,2-dicyanocyclobutene was added at such a rate as to maintain the low pressure; 2.7 g of 1-cyanocyclobutene (**12**) was collected in the trap, 60% yield. The product (pure by NMR) was used in the photolysis without further purification: IR (neat) 2240 cm^{-1}; NMR ($CDCl_3$) δ 6.75 (1 H, t, $J \sim 1$ Hz), 2.85 (2 H, t, $J = 3.5$ Hz), 2.6 (2 H, m).

Attempted Photocyclization of 10. Photolyses were carried out in an quartz apparatus (Ace Glass) using a 450-W Hanovia immersion lamp. Irradiation for 10–72-h times caused disappearance of starting material **10** as evidenced by GLC and NMR (cyclobutene proton at δ 6.72). Concentrations of 0.2–0.02 M **10** in cyclohexane, diisopropyl ether, THF, acetone, and CH_2Cl_2 were used but no **4** could be detected by direct comparison with authentic material. NMR, IR, and mass spectral evidence was consistent with simple photodimerization of **10.**

1,9,9-Trimethyl-5-carbomethoxytricyclo[4.4.0.$0^{2,5}$]decan-7-one (3). Isophorone (250 mg) in 10 mL of dichloromethane was degassed following the addition of 1/3 equiv of methyl cyclobut-1-enecarboxylate (0.7 M solution in dichloromethane). The resulting solution was irradiated with a 450-W Hanovia photochemical reactor (Pyrex filter) at room temperature for 1 h. Thereafter, an additional 1/3 equiv of methyl cyclobut-1-enecarboxylate was added, and the resulting solution was degassed and irradiated for 1.5 h until 1 2/3 equiv of methyl cyclobut-1-enecarboxylate had been added. The reaction mixture was concentrated under reduced pressure and was heated to 70 °C (0.5

Table V. Crystal and Diffractometer Data

empirical formula	$C_{15}H_{17}O_2$ (**15**)	$C_{14}H_{20}O$ (**4**)
color of crystal	colorless	colorless
crystal dimensions	~0.2 × 0.3 × 0.3 mm	~0.04 × 0.5 × 0.55 mm
space group	$P2_1$	$P2_1$
cell dimensions	(at −135 °C; 14 reflections)	(at −170 °C; 15 reflections)
a	12.211 (2) Å	8.951 (2) Å
b	6.371 (2) Å	10.428 (4) Å
c	8.796 (3) Å	6.368 (3) Å
β	111.65 (3)°	98.49 (3)°
Z (molecules/cell)	2	2
volume	636.02 Å^3	587.88 Å^3
calcd density	1.234 g/cm^3	1.245 g/cm^3
wavelength used	0.710 69 Å	0.710 69 Å
mol wt	236.35	220.31
linear absorption coefficient	0.742 cm^{-1}	0.758 cm^{-1}
detector to sample distance	22.5 cm	22.5 cm
sample to source distance	23.5 cm	23.5 cm
takeoff angle	2°	2°
av ω scan width at half-height	0.25°	0.25°
data collection using standard moving crystal-moving detector technique with the following values:		
scan speed	2.5°/min	3°/min
scan width	2° + dispersion	2° + dispersion
single background time at extremes of scan	10 s	10 s
aperture size	2.5 × 3 mm	3 × 4 mm
limits of data collection		
min 2θ	4°	4°
max 2θ	55°	45°
total no. of reflections collected	1649	2520
no. of unique intensities	1599	1424
no. with $F > 0.0$	1559	1409
no. with $F > \sigma(F)$	1409	1247
no. with $F > 2.33\ \sigma(F)$	1259	857
Final residuals: $R(F)$	0.053	0.102
$R_w(F)$	0.046	0.081
Goodness of fit for the last cycle	0.96	1.15
max δ/σ for last cycle	0.05	0.1

mm) for 1 h. Preparative thin layer chromatography (10/90 ether-pentane) gave 265 mg (58%) of 1,9,9-trimethyl-5-carbomethoxytricyclo[4.4.0.0^{2,5}]decan-7-one (**3**): 2,4-dinitrophenyhydrazone mp 125–126 °C; IR (film) 1718, 1669 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (3 H, s), 1.42 (3 H, s), 1.16 (3 H, s), 1.06 (3 H, s), 2.40–3.30 (10 H, m); mass spectrum *m/e* (% base) 250 (3), 165 (40), 139 (41), 107 (38), 83 (51), 82 (100), 55 (52), 41 (62). Calcd for $C_{15}H_{22}O_3$: mol wt, 250.1570. Found: mol wt, 250.1586.

1,9,9-Trimethyl-5-cyanotricyclo[4.4.0.0^{2,5}]decan-7-one (16). Isophorone **2** (1.9 g, 14 mmol) and 1.1 g (14 mmol) of 1-cyanocyclobutene (**12**) were irradiated for 15 h in 15 mL ether and 30 °C. The ether was then removed under vacuum and the residue heated at 90 °C (0.15 mm) for 1 h to remove unreacted isophorone or volatile byproducts. Then **16** was distilled at ~135 °C (0.1 mm), giving 1.43 g (47% yield): IR (neat) 3125–2857, 2257, 1715 cm^{-1}; NMR ($CDCl_3$) δ 3.1–2.0 (8 H, m), 1.75 (2 H, bs), 1.3 (3 H, s), 1.1 (3 H, s), 0.98 (3 H, s); mass spectrum *m/e* (% base) 217 (1), 139 (35), 83 (16), 82 (32), 73 (25), 55 (18), 45 (47), 43 (27), 41 (24), 32 (100). Calcd for $C_{14}H_{19}NO$: mol wt, 217.1468. Found: mol wt, 217.1450.

Preparation of 4. Method A. 1,9,9-Trimethyl-5-carbomethoxytricyclo[4.4.0.0^{2,5}]decan-7-one (250 mg) (**3**) was dissolved in 10 mL of ethanol and treated with 50 mg of sodium borohydride. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was added to 25 mL of dilute hydrochloric acid and stirred at room temperature for 2 h. The mixture was extracted into ether. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated under reduction pressure to give an oil. Pentane (1 mL) was added to the oil and was cooled in dry ice. The resulting crystals were dissolved in 1 mL of hot pentane and then kept at −15 °C overnight. Two crops of crystals were obtained in this manner. Total yield of lactone **4** was 70 mg (32%): mp 77.5–78.5 °C; IR (CCl_4) 1754 cm^{-1}; NMR ($CDCl_3$) δ 4.85 (1 H, m), 1.30 (3 H, s), 1.09 (3 H, s), 1.00 (3 H, s), 1.20–3.20 (10 H, m); mass spectrum *m/e* (% base) 220 (5), 191 (32), 135 (44), 121 (37), 107 (32), 96 (39), 91 (35), 68 (100), 41 (54). Calcd for $C_{14}H_{20}O_2$: 220.1464. Found: mol wt, 220.1454.

Method B. 16 (0.723 g, 3.3 mmol) in 10 mL of ether was added to 0.035 g (1 mmol) of $NaBH_4$ in 5 mL of ethanol at 0 °C over 15 min. The mixture was stirred at 0 °C for 1.5 h, then at room temperature overnight. The reaction mixture was acidified with 10 mL of 5% HCl and the ethanol evaporated. The residue was refluxed with 20 mL of 3 N HCl in 10 mL of ethanol for 4 h. After extraction with ether, washing with water, and drying over Na_2SO_4 the solvents were evaporated. Preparative TLC (50/50 ether-pentane) gave 86 mg (12% yield) of lactone **4**: mp 78–79 °C.

1-Methyl-5-cyano-8-isopropyltricyclo[4.4.0.0^{2,5}]decan-7-one (17). Piperitone **20** (1.26 g, 8.3 mmol) and 0.66 g (8.3 mmol) of 1-cyanocyclobutene (**12**) in 15 mL of ether was irradiated overnight at room temperature. The ether was then evaporated and the crude product kept at 90 °C (0.1 mm) for 1 h. Distillation at 150 °C (0.1 mm) gave 0.735 g (38%) of compound **17**: IR (neat) 3096–2841, 2242, 1709 cm^{-1}; NMR ($CDCl_3$) δ 3.0–1.7 (13 H, m), 1.2 (3 H, s), 0.98 (3 H, d, J = 7 Hz), 0.85 (3 H, d, J = 7 Hz); mass spectrum *m/e* (% base) 231 (5), 153 (56), 145 (47), 133 (60), 119 (78), 118 (48), 110 (64), 109 (40), 104 (45), 91 (41), 82 (50), 79 (45), 71 (48), 67 (41), 55 (78), 43 (100). Calcd for $C_{15}H_{21}NO$: mol wt 231.1624. Found: mol wt, 231.1656.

1-Methyl-5-carbomethoxy-8-isopropyltricyclo[4.4.0.0^{2,5}]decan-7-one (14). Piperitone **13** (250 mg) in 10 mL of dichloromethane was degassed following the addition of 1/3 equiv of methyl cyclobut-1-enecarboxylate (0.7 M solution in dichloromethane). The resulting solution was irradiated in a 450-W Hanovia photochemical reactor (Pyrex filter) at room temperature for 1 h. Thereafter, an additional 1/3 equiv of methyl cyclobut-1-enecarboxylate was added, and the resulting solution was degassed and irradiated for 1 h until 1 2/3 equiv of methyl cyclobut-1-enecarboxylate had been added. The reaction mixture was concentrated under reduced pressure and heated to 70 °C (0.5 mm) for 1 h. Preparative thin layer chromatography (10/90 ether-pentane) gave 214 mg (49%) of 1-methyl-5-carbomethoxy-8-isopropyltricyclo[4.4.0.0^{2,5}]decan-7-one (**14**): NMR ($CDCl_3$) δ 3.64 (3 H, s), 1.23 (3 H, s), 0.070–3.30 (18 H, m); mass spectrum *m/e* (% base) 264 (10), 178 (55), 152 (65), 107 (61), 93 (63), 91 (53), 81 (52), 55 (83). Calcd for $C_{16}H_{24}O_3$: mol wt, 263.1727. Found: mol wt, 264.1714.

Preparation of 15. Method A. 14 (220 mg, 0.8 mmol) was treated

with 50 mg (1.3 mmol) of $NaBH_4$ in 5 mL of ethanol at 0 °C for 1 h. Then 20 mL of 10% HCl was added and stirring was continued for an additional 1 h. The reaction mixture was then extracted with ether, washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent and preparative TLC (10% ether-90% petroleum ether) gave 19 mg (10%) of lactone **15.**

Method B. 17 (0.135 g, 0.6 mmol) and 0.035 of g $NaBH_4$ (1 mmol) were stirred overnight in 10 mL of ethanol. The mixture was acidified with 10 mL of 5% HCl and the ethanol evaporated. The residue was extracted with 45 mL of ether and the ether layer washed with water, dried over Na_2SO_4, and evaporated to yield after preparative TLC 0.077 g (57%) of lactone **15:** mp 80-81.5 °C; IR (CCl_4) 3030-2817, 1730 cm^{-1}; NMR ($CDCl_3$, 220 MHz) δ 4.54 (1 H, d, J = 9 Hz), 2.61 (2 H, m), 2.43 (1 H, d, J = 9 Hz), 2.0-2.27 and 1.2-1.64 (9 H, m), 1.16 (3 H, s), 0.93 (3 H, d, J = 7 Hz), 0.89 (3 H, d, J = 7 Hz); mass spectrum *m/e* (% base) 234 (9), 191 (20), 165 (18), 164 (32), 147 (24), 137 (20), 123 (26), 122 (26), 121 (40), 107 (28), 105 (30), 97 (38), 95 (36), 93 (51), 82 (39), 81 (100), 69 (91), 68 (78), 67 (53), 55 (74), 53 (37), 31 (96). Calcd for $C_{15}H_{22}O_2$: mol wt, 234.1621. Found: mol wt, 234.1626.

(*Z,E*)-6-Hydroxygermacra-1(10),4-dien-15-oic Acid δ-Lactone (22). A solution of 47 mg (0.2 mmol) of **15** in 1 mL of benzene was heated in a sealed tube at 180 °C for 1 h. GC-MS indicated at ratio **22** to **23** of 78:22. Preparative TLC of the product (25/75 ether-petroleum ether) gave 29 mg (62%) of compound **22:** IR (CCl_4) 3125-2924, 1764, 1538, 1247, 867 cm^{-1}; NMR ($CDCl_3$) δ 7.19 (1 H, s), 5.23 (1 H, m), 5.07 (1 H, t, J = 6 Hz), 1.6-2.4 (10 H, m), 1.59 (3 H, s), 1.09 (3 H, d, J = 6 Hz), 1.01 (3 H, d, J = 6 Hz); NMR (CCl_4) δ 7.02 (1 H, s), 5.09 (1 H, m), 5.02 (1 H, t, J = 6 Hz), 1.6-2.4 (10 H, m), 1.59 (3, H, s), 1.09 (3 H, d, J = 6 Hz), 1.01 (3 H, d, J = 6 Hz); mass spectrum *m/e* (% base) 234 (6), 145 (14), 123 (17), 121 (40), 119 (100), 117 (98), 97 (22), 93 (25), 82 (50), 81 (37), 69 (43), 68 (36), 67 (30), 55 (40), 41 (69). Calcd for $C_{15}H_{22}O_2$: mol wt, 234.1621. Found: mol wt, 234.1611.

Experimental Crystallography. Low-temperature single-crystal studies were performed for **4** and **15.** The diffractometer used was locally constructed[31,32] and consisted of a Picker goniostat interfaced to a TI980 minicomputer. The goniostat was equipped with an incident beam monochromator (highly oriented graphite crystal, 002 plane), and suitable crystals were mounted on a glass fiber with silicone grease and characterized directly on the goniostat, using reflection data obtained from a systematic search of reciprocal space. Cell dimensions and alignment were determined from angular data obtained with an automated top/bottom-left/right slit assembly using data in both the positive and negative regions of 2θ. Crystal and diffractometer data are listed in Table V for both compounds.

The structures were solved by direct methods and Fourier techniques[27] and refined by a full-matrix least-squares treatment. In both molecules hydrogen positions were located and refined isotropically.

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Supplementary Material Available: Figure 1 (ORTEP drawing of **4**), Figures 3 and 4 (numbering schemes for tables), Table I (dihedral angles and coupling constants for **4** and **15**), Table II (C-C distances for bicyclo[2.2.0]hexanes), Table III ("pucker" angles for bicyclo[2.2.0]hexanes), Table IV (best molecular fit of **15** (A) with other bicyclo[2.2.0]hexanes (B)), Tables VI-XI (crystallographic data for **4**), Tables XII-XVII (crystallographic data for **15**), and Table XVIII (derived Cartesian coordinates for **18**) (50 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For part 2 in this series see ref 2b. Contribution No. 3167 from the Department of Chemistry, Indiana University, Bloomington, Ind. Taken in part from the M.S. Thesis of L. R. Phillips, Indiana University, Sept 1977.

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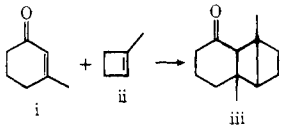

i ii iii

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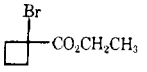

iv

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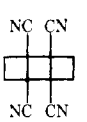

v

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General-Base-Catalyzed Intramolecular Aminolysis of Thiol Esters. Cyclization of *S*-*n*-Propyl *o*-(2-Imidazolyl)thiolbenzoate. Relationship of the Uncatalyzed and Base-Catalyzed Nucleophilic Reactions

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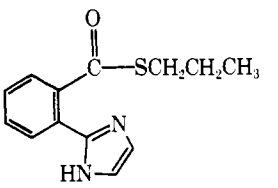
Abstract: Rate constants have been obtained at 30 °C in H_2O for hydrolysis of *S*-*n*-propyl *o*-(2-imidazolyl)thiolbenzoate. The reaction involves rapid formation and subsequent breakdown of an acylimidazole intermediate. A plot of log k_0 for cyclization vs. pH is linear with a slope of 1.0 at all pH values. The contributions to k_0 of the uncatalyzed neutral species and apparent hydroxide ion catalyzed reactions are equal at the pK_a of the nucleophile. The kinetic data indicate that cyclization to a tetrahedral intermediate is an equilibrium step, breakdown of the tetrahedral intermediate being rate determining. The value of k_{OH} for cyclization of the thiol ester is 5×10^6 greater than for hydrolysis of *n*-propyl thiolbenzoate. In comparison with bimolecular attack of imidazole on *n*-propyl thiolbenzoate the effective molarity of the neighboring imidazolyl neutral species is 1.6×10^3 M while that of the imidazolyl anion is 7×10^2 M. General base catalysis is observed in the intramolecular nucleophilic reaction. The value of the Brønsted coefficient β is 1.0, indicating that the rate-determining step is a proton transfer in the thermodynamically unfavorable direction. This step may be proton abstraction by the base from a neutral tetrahedral intermediate. This relationship appears to be general for intramolecular aminolysis reactions in the 2-substituted benzoate system.

Both intramolecular and bimolecular aminolyses of esters have been extensively studied.[1-9] Intramolecular aminolysis of 2-substituted benzoate esters having poor leaving groups (pK_a = 10–16) proceeds with striking mechanistic differences in comparison with analogous bimolecular reactions.[8,9] Neighboring aminomethyl and imidazole nucleophiles in the 2-substituted benzoate esters give rise to intramolecular reactions which are characterized by linear plots of the logarithms of the rate constants vs. pH, showing hydroxide ion catalysis of the nucleophilic reaction (or the kinetically equivalent reaction of the anionic species). In the case of neighboring imidazole displacement of trifluoroethanol or phenol leaving groups,[9] an uncatalyzed neutral species reaction also occurs. Brønsted plots for general base catalysis have slopes of 1.0, which indicate that a proton transfer in the thermodynamically unfavorable direction is rate determining.[10] This step is most likely proton transfer to or from the tetrahedral intermediate. A number of extremely important questions have arisen as a result of the studies of intramolecular reactions of the 2-substitued benzoate esters.[8,9,11] Among these are (1) What is the general relationship between the neutral species and OH^--catalyzed nucleophilic reactions and how is it influenced by leaving group? (2) What is the mechanistic significance of the buffer catalysis that has been observed? Why is it found in the 2-substituted benzoate system and apparently not in other intramolecular systems that have previously been studied?[12-14] (3) Is the Brønsted β value of 1.0 a general feature of these reactions?

If the mechanistic differences in the intramolecular aminolysis reactions of 2-substituted benzoate esters in comparison with similar bimolecular aminolysis reactions are due to proximity of the nucleophile and the carbonyl in the intramolecular system, then similar differences might also exist in the reactions of 2-substituted benzoate esters and corresponding *intramolecular* reactions where degrees of freedom exist for rotation of the nucleophile away from the carbonyl. To determine whether this is the case in the intramolecular reactions of thiol esters, we have studied the hydrolysis of *S*-*n*-propyl *o*-(2-imidazolyl)thiolbenzoate (I). The intramolecular nucleophilic reaction of *S*-*n*-propyl γ-(4-imidazolyl)-thiolbutyrate,[12] having the same entering and leaving groups as I but in which the nucleophile is not rigidly held adjacent to the carbonyl, occurs through attack by the neutral species without buffer catalysis. In contrast we have found that I cyclizes through attack by both the neutral and anionic species (or a kinetic equivalent) with pronounced general base catalysis.



I

The mechanism of neighboring imidazole participation in the hydrolysis of thiol esters in constrained systems is of great interest in view of the fact that a number of protease enzymes such as papain have both cysteine and histidine in the active site, and histidine may participate in the hydrolysis of the acyl–thiol intermediate.[15]

Experimental Section

***S*-*n*-Propyl o-(2-imidazolyl)thiolbenzoate hydrochloride (I)** was prepared by heating at reflux 2 g of *N*,2-(2′-benzoyl)imidazole[9] with a concentrated solution of *n*-propyl mercaptan in tetrahydrofuran for 6 h. The solvent and excess thiol were removed at low pressure and

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