Cyclizations to Lactones. ^{18}O Mechanism Study

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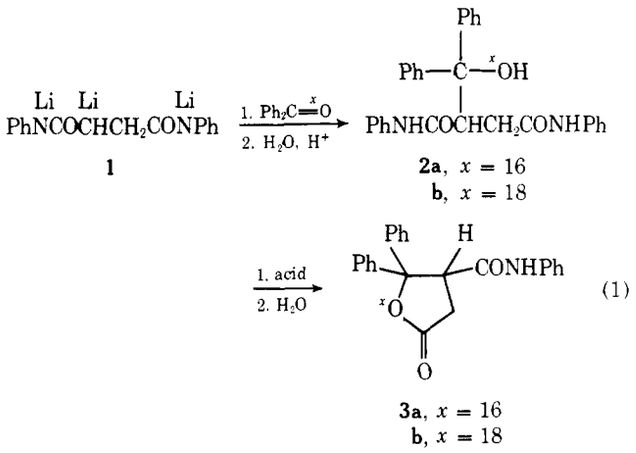
^{18}O was incorporated into the hydroxyl oxygen of 2-(1,1-diphenyl-1-hydroxymethyl)succinanilide (2), which was subsequently treated with concentrated sulfuric acid (a), refluxing acetic acid (b), and methanolic hydrogen chloride (c). The resulting cyclization product, 4,4-diphenyl-3-carboxanilidebutanolactone (3), exhibited complete elimination (a) or retention (b and c) of ^{18}O. These results indicate that both a carbonium ion mechanism (a) or an intramolecular (A-2) acyl substitution mechanism (b and c) can account for the formation of lactone 3.

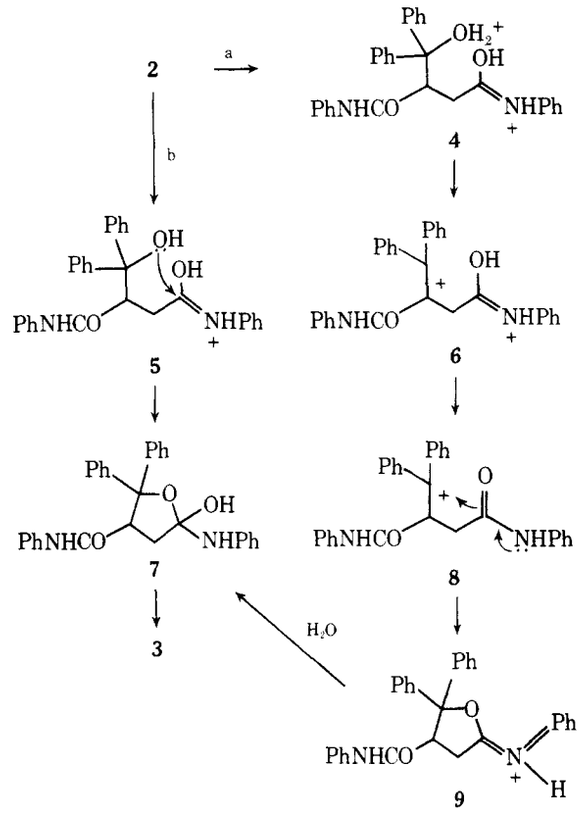
Benzophenone and 1,3,6-trilithiosuccinanilide (1) were condensed to afford **2a**,[1] which was subsequently treated with refluxing acetic acid, methanolic hydrogen chloride, or cold concentrated sulfuric acid (eq 1). All three acid systems effected cyclization to 4,4-diphenyl-3-carboxanilidebutanolactone (**3a**) in high yield, 92, 89, and 91%, respectively. A single mechanism consistent with these results would be difficult to formulate considering the dehydrating properties of concentrated sulfuric acid vs. the proton donating characteristics of acetic acid or methanolic hydrogen chloride. Two basic mechanisms could be designed for these observations (Scheme I). One, path a, would entail carbonium ion formation (**6**) with its subsequent capture by the oxygen of the amide carbonyl[2] upon pouring the reaction mixture onto ice. The incipient water would then hydrolyze the resulting imino lactone (**9**) to give **3**.[3] An alternative mechanism, path b, is an intramolecular (A-2) acyl substitution.[4]



Distinguishing between these mechanisms could be effected by incorporation of an oxygen label in the hydroxyl of **2** with subsequent mass spectral analysis. Cyclization via path b would result in the oxygen label being located in the ether linkage of **3**, whereas the label would be lost via carbonium ion formation in path a.

Benzophenone-^{18}O (**11**), synthesized by hydrolyzing its imine hydrochloride (**10**) in water-^{18}O, was reacted with 1,3,6-trilithiosuccinanilide (1) to form the ^{18}O-carbinol **2b**. The resulting diphenylmethyl carbinol **2b**, with its hydroxyl oxygen containing 21.8% ^{18}O, was subsequently treated with the various acid systems, the lactone products being analyzed by mass spectrometry (Table I). No oxygen label was retained in the lactone when **2b** was treated with cold concentrated sulfuric acid. This reaction proceeded via a carbonium ion (**6**) as outlined in path a. In contrast, there was complete retention of the hydroxyl oxygen when the labeled carbinol **2b** was refluxed with acetic acid or treated with methanolic hydrogen chloride (Table I). These results demonstrate that acyl substitution (path b) is the mechanism of this cyclization reaction.

Scheme I



Mass Spectral Analysis. A fragmentation pathway as outlined in Scheme II demonstrated the presence of the oxygen label in the sets of peaks for *m/e* 183 (**12**) and *m/e* 105 (**13**). The oxygens of these species originated from the ether linkage of **3b** (Table II) and contained 91 (via acetic acid) and 87.2% (via methanolic hydrogen chloride) of the ^{18}O. The remaining 9 and 12.8%, respectively, of the oxygen label was contained in the set of ions at *m/e* 175, the base peak. This fragment contains the lactone carbonyl oxygen, and arises directly from the molecular ion by the loss of benzophenone ($M^+ - m/e$ 182).[5] For **3b**, it would be reasonable to expect that the oxygen

Scheme II

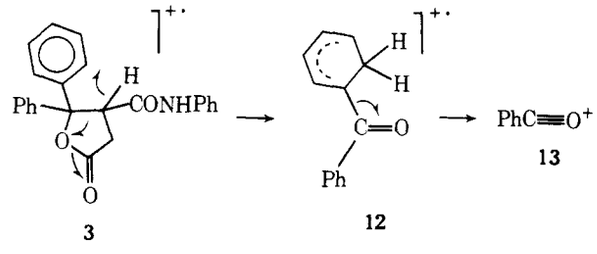
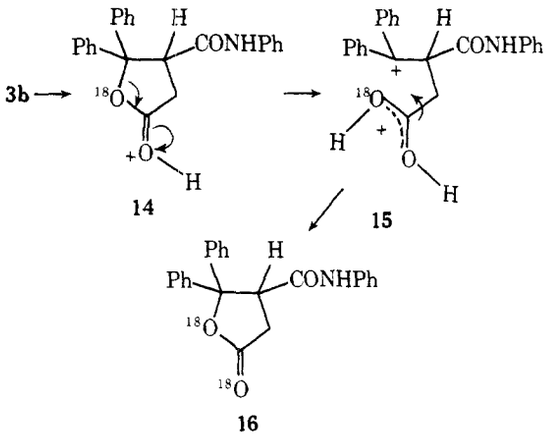


Table I. ^{18}O Analysis

	% ^{18}O[a]	% retention
^{18}O-carbinol **2b**	21.8	
Lactone via		
H_2SO_4 (**3a**)	0.0	0
CH_3COOH (**3b**)	21.8[b]	100
CH_3OH/HCl (**3b**)	21.7	>99

[a] The set of peaks containing the molecular ion was used for these calculations. [b] In the sequence **2b** (via acetic acid) to **3b** to **16**, the mass spectra of both **2b** and **16** analyze for 21.8% ^{18}O. It is therefore assumed that **3b** also contains the same amount of ^{18}O label, even though its mass spectra analyze for 21.4% ^{18}O.

Scheme III



label present in the set of ions at *m/e* 175 comes about by scrambling in the mass spectrometer.[6]

The mass spectrum of the product (**16**) resulting from the treatment of **3b** with concentrated sulfuric acid (Scheme III) gave corroborative evidence for the above fragmentation pathways. The peaks corresponding to *m/e* 175 and 105 analyze for 54.8 and 45.2% of the oxygen label, respectively. This indicates that the ether oxygen of **3b** equilibrated with the lactone carbonyl oxygen. That the oxygen label is not evenly distributed in the mass spectral fragments of **16** is indicative of about 9.6% scrambling in the mass spectrometer[6] and is consistent with the average of 10.9% scrambling in the mass spectra of **3b** (Table II).[7]

Mechanistic Analysis. The above reaction sequence (Scheme III) also provided insight into the reaction mechanism in sulfuric acid. The diphenylmethyl carbonium ion (**15**) should be analogous to the corresponding ion (**6**) of Scheme I. Upon quenching these carbonium ion intermediates by pouring onto ice, they are captured by the relatively nucleophilic carbonyl oxygens and not by the incipient water. This eliminates the possibility of carbonium ion **6** from capturing a molecule of water and cyclizing via path b. Cyclization with refluxing acetic acid or methanolic hydrogen chloride must occur via an intramolecular A-2 mechanism (path b), the reacting species being expected to be the oxygen-protonated anilide **5**.

Experimental Section

Melting points were recorded on a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately before use. Low resolution mass spectra were obtained by Mr. Fred Williams at the Research Triangle Institute for Mass Spectrometry, Research Triangle Park, N.C., on a MS-902 mass spectrometer. Elemental analysis were performed by M-H-W Laboratories, Garden City, Mich. and Janssen Pharmaceutica, Beerse, Belgium.

2-(1,1-Diphenyl-1-hydroxymethyl)succinanilide (2a). *N*-Butyllithium in hexane (28 mL, 63 mmol) was added dropwise over 30 min under nitrogen to a cooled (0–5 °C) suspension of 5.4 g (20 mmol) of succinanilide in 125 mL of THF. After stirring the clear yellow-orange solution for 10 min, the dropwise addition of 4.2 g (23 mmol) of benzophenone dissolved in 50 mL of THF was made over 5 min. The resulting dark blue mixture was stirred (0–5 °C) for 1 h before pouring it onto 100 mL of a 2 N HCl–ice mixture (1:1 by volume). The organic layer was separated and the aqueous phase saturated with NaCl before extraction with three 100-mL portions of ether. The combined organic extracts were dried (Na_2SO_4) and evaporated. The resulting solid was recrystallized from methanol, giving 4.4 g (49%) of **2a**, mp 218–219.5 °C. One recrystallization ($EtOH-H_2O$) gave an analytical sample, mp 218–219.5 °C; mass spectrum, *m/e* (relative intensity): 450 (4), 358 (5), 316 (69), 268 (18), 193 (35), 182 (69), 176 (100), 148 (35). Anal. Calcd for $C_{29}H_{26}N_2O_3$: C, 77.31; H, 5.81; N, 6.21. Found C, 77.23; H, 5.76; N, 6.22.

Benzophenone Imine Hydrochloride (10). To 120 mL of sodium-dried benzene at room temperature, a mixture of 10 g (100 mmol) of tetramethylethylenediamine and 45 mL (100 mmol) of *n*-butyllithium in hexane was added over 30 min. The yellow solution was stirred for 3 h, after which time it was assumed to contain 100 mmol of phenyllithium. To this solution was added 10 g (100 mmol) of benzonitrile in 25 mL of sodium-dried hexane, and the mixture was stirred for 1 h. The resulting dark brown solution was poured onto 200 mL of ice–water. The organic layer was separated, the aqueous layer being twice extracted with 100-mL portions of ether. The combined organic fractions were dried (Na_2SO_4) and evaporated to give an oil. The oil, as indicated by its infrared spectrum, was a mixture of benzophenone and the desired benzophenone imine. Separation was effected by pouring the oil into 100 mL of cold (0–5 °C) 2 N HCl. The resulting crystals of benzophenone imine hydrochloride (**10**) were filtered and dried, 14.7 g (68%), and used without further purification.

Benzophenone-^{18}O (11). A solution of 1.5 g (8.3 mmol) of benzophenone imine hydrochloride (**10**) in 5 mL of 20% water-^{18}O (obtained from Diaprep Inc., Atlanta, Ga.) was refluxed for 1.5 h. The resulting oil was repeatedly extracted with ether by pipet. This procedure was repeated several times upon addition of **10** to the water-^{18}O. The subsequent ether extracts were combined, dried (Na_2SO_4), and evaporated to an oil. Crystallization was effected by seeding to give **11**, mp 47–49 °C. Benzophenone-^{18}O obtained in this manner was used without further purification.

2-(1,1-Diphenyl-1-hydroxymethyl-^{18}O)succinanilide (2b). This reaction was performed on one-half scale as that of **2a**, 10 mmol of **1** in 75 mL of THF being formed before 2.1 g (11.5 mmol) of **11** in 25 mL of THF was added over 4 min. Stirring for 1 h preceded inverse neu-

Table II. Mass Spectral Data of ^{18}O Containing Fragments

	% ^{18}O		% M^+[c]		% norm[d]	
Fragment	*m/e* 175[a]	*m/e* 105[b]	*m/e* 175[a]	*m/e* 105[b]	*m/e* 175[a]	*m/e* 105[b]
Lactone **3b** via						
CH_3COOH	2.0	20.2	9.3	94.4	9.0	91.0
CH_3OH/HCl	2.6	17.7	12.0	81.6	12.8	87.2
Lactone **16**[e]	12.1	10.0	55.5	54.9	54.8	45.2

[a] The set of peaks for the base peak containing the lactone **3b** carbonyl oxygen. [b] The set of peaks for the benzoyl fragment containing the ether oxygen of **3b**. [c] Retention of the oxygen label relative to that in the molecular ion. [d] Normalization, as determined by totaling the ^{18}O of the set of peaks at *m/e* 175 and 105 and setting this equal to 100% ^{18}O. [e] From the molecular ion **16** was calculated to contain 21.8% ^{18}O.

tralization. Upon workup, the resulting solid was recrystallized (EtOH), affording the desired **2b**, 1.9 g (42%), mp 217–219 °C.

Cyclization of 2a and 2b with Sulfuric Acid. In a typical reaction, 1.0 g (2.22 mmol) of **2a** was dissolved by manipulation and stirring with a glass rod in 15 mL of cold (0–5 °C) concentrated sulfuric acid. Upon standing 1 h **3a** was precipitated from the resulting solution by pouring onto 100 g of ice. Melting allowed for collection of the precipitate, and gave 0.73 g (92%) of **3a**, mp 210–213 °C. One recrystallization (EtOH) gave the analytical sample, mp 220–222 °C: mass spectrum, *m/e* (relative intensity) 357 (15), 175 (100), 147 (34), 146 (30), 119 (18), 105 (36), 93 (50), 91 (15); *m*/e* 123.5, 121.8, 98.5, 85.7, 59.2, 56.5. Anal. Calcd for $C_{29}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.06; H, 5.43; N, 3.83. The yield of **3a** from **2b** was 81%.

Cyclization of 2a and 2b by Refluxing Acetic Acid. In a typical reaction, a mixture of 10 mL of acetic acid and 0.75 g (1.66 mmol) of **2b** was refluxed for 1 h. Upon cooling, **3b** was precipitated from the resulting solution by pouring onto 50 g of ice. The precipitate was collected to give 0.51 g (86%) of **3b**, mp 215–218 °C. One recrystallization (EtOH) gave a sample melting at 218–220 °C. The yield of **3a** from **2a** was 89%.

Cyclization of 2a and 2b by Methanolic Hydrogen Chloride. In a typical reaction, $HCl_{(g)}$ was bubbled into a stirred solution of 0.75 g (1.66 mmol) of **2b** in 100 mL of absolute methanol for about 30 min. The solution was evaporated to 25 mL before pouring onto an equal volume of cold (0–5 °C) water. The resulting precipitate was collected and recrystallized (EtOH) affording **3b**, 0.47 g (79%), mp 218–220 °C. The yield of **3a** from **2a** was 91%.

Treatment of 3b with Sulfuric Acid. In 2 mL of cold (0–5 °C) concentrated sulfuric acid, 30 mg (66.6 μmol) of **3b** was dissolved by stirring with a glass rod. After standing 5 min, **16** was precipitated from the solution by adding 20 g of crushed ice. The precipitate was collected and gave 28 mg (93%), mp 120–170 °C. One recrystallization ($EtOH-H_2O$) afforded pure **16**, mp 217–218 °C.

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Registry No.—**2a**, 23105-20-6; **2b**, 62861-49-8; **3a**, 23105-22-8; **3b**, 62905-90-2; **10**, 5319-67-5; **13**, 62861-50-1; **16**, 62905-91-3; succinanilide, 15510-09-5; benzophenone, 119-61-9; tetramethylethylenediamine, 110-18-9; benzonitrile, 100-47-0.

References and Notes

(1) T. C. Adams, Jr., and C. R. Hauser, *Chem. Ind. (London)*, 697 (1969).
(2) R. F. Raffauf, *J. Am. Chem. Soc.*, **74**, 4460 (1952). P. N. Craig, *ibid.*, **74**, 129 (1952).
(3) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965).
(4) T. Yamana, A. Tsuji, and Y. Mizukami, *Chem. Pharm. Bull.*, **20**, 1217 (1972). R. B. Martin, R. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 158 (1964).
(5) The metastable peak for this fragmentation and subsequent fragmentations in this sequence are contained in the Experimental Section.
(6) J. H. Beynon, R. M. Caprioli, R. H. Shapiro, K. B. Tomer, and C. W. J. Chang, *Org. Mass. Spectrom.*, **6**, 863 (1972).
(7) It is of significance that scrambling of the label does not occur during the cyclization reaction and that the hydroxyl oxygen of **2** is specifically located in the ether linkage of **3**.

Stereochemistry of the Cycloaddition Reaction of Methylcarbenoid of Zinc to Cyclic Allylic Alcohols

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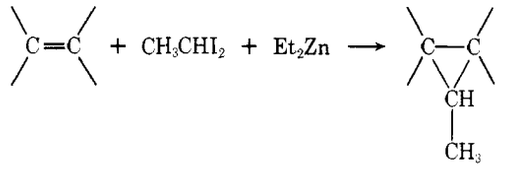
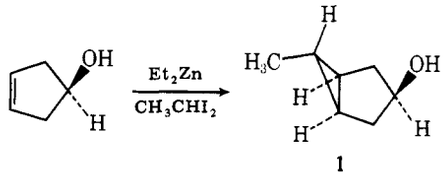
Stereochemistry of the cycloaddition reaction of the methylcarbenoid of zinc to 2-cyclohexen-1-ol, 2-cyclohepten-1-ol, and *cis*-2-cycloocten-1-ol was investigated under two conditions: (A) equimolar amounts of diethylzinc and cyclic allylic alcohol were used; and (B) twice as much diethylzinc as the alcohol by mole was used. Intramolecular ethylidene transfer reaction in an intermediate like **20**, and a quasi-intermolecular ethylidene transfer reaction in an intermediate like **22**, were considered to be predominant under the conditions A and B, respectively. However, with respect to the configuration of the cyclopropane ring with hydroxyl group in the products, highly syn- or anti-selective cycloadditions were observed independently of the two reaction conditions. On the other hand, with respect to the configuration of the methyl group introduced by the organozinc reagent, the stereoselectivity depended upon the two reaction conditions, and the steric restraint caused by the hydroxyl group on the configuration of the methyl group was concluded to be relatively loose under the condition of a quasi-intermolecular ethylidene transfer reaction in an intermediate like **22**.

In a previous paper,[1] we have demonstrated the synthesis of methylcyclopropane derivatives by the reaction of olefins with 1,1-diiodoethane and diethylzinc (eq 1). The reaction



(1)

proceeds stereospecifically, i.e., cis and trans olefins afford cyclopropane derivatives whose configurations with respect to the substituents from original olefins are cis and trans, respectively. With respect to the stereochemistry of the methyl group introduced by the organozinc reagent, the reaction generally yields the endo or cis isomers predominantly over the corresponding exo or trans isomers, respectively. For example, the reaction with cyclohexene gave a 1.5:1 mixture of *endo*- and *exo*-7-methylbicyclo[4.1.0]heptane. On the other hand, the exo or trans isomers were obtained predominantly over the corresponding endo or cis isomers, respectively, from olefins containing hydroxyl group such as allyl alcohol and 2-buten-1-ol. The stereochemistry of the reaction with 3-cyclopenten-1-ol was especially interesting, which gave exclusively *exo*-6-methyl-*cis*-3-hydroxybicyclo[3.1.0]hexane (**1**) among four possible stereoisomers. This work was aimed at



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