

A Novel Method for the Degradation of the Carbon Chain of Organic Acids and Their Derivatives

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Received December 6, 1972

A convenient scheme for the stepwise degradation of ethyl caprylate (1) is described, which allows the removal of either one, two, or three carbon fragments from the chain, affording high yields of the corresponding carbonyl compounds. The method may have important applications in the transformations of steroids, lipids, and other natural products.

The utility of side chain degradative schemes in the syntheses, modification, and structural elucidation of natural products is well known.² The same type of reactions also find useful applications in the transformations of lipids.³ However, none of the available methods⁴⁻⁸ for degrading carboxylic acids give particularly attractive yields.

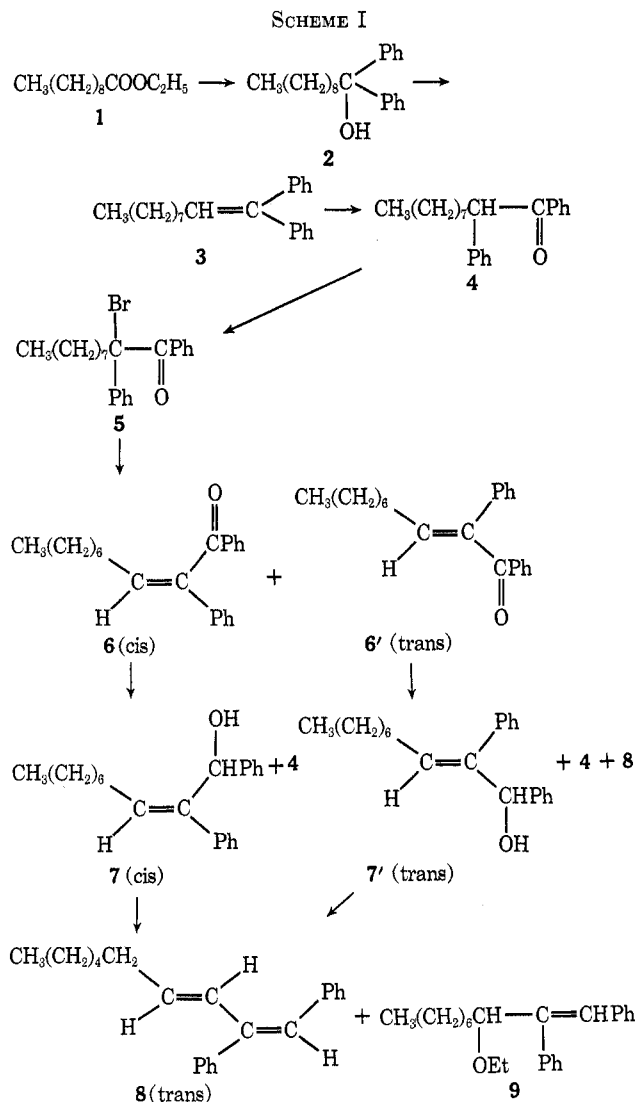
Furthermore, to our best knowledge, there is no satisfactory degradative scheme which permits the elimination of two carbon atoms at a time. The present paper describes a practical and flexible procedure for removing one, two, or three carbon atoms. The key step makes use of a rearrangement worked out before⁹ and found to be successful on a variety of substrates, including some steroids. The individual steps in the degradative sequence are outlined in Scheme I.

Results and Discussion

A commercial sample¹⁰ of pure (99% by glc) ethyl caprylate (1) was allowed to react with an ether solution of phenylmagnesium bromide, prepared in the usual way. After purification of the crude alcohol by column chromatography, a nearly quantitative yield (96%) of 1,1-diphenyl-1-decanol (2) was obtained. Dehydration of the alcohol was achieved in refluxing acetic anhydride. After suitable work-up and purification of the crude product by column chromatography, a sufficiently pure sample of 1,1-diphenyl-1-decene (3) was obtained. The yield based on the ester 1 was 85%. The identity of the product was confirmed by infrared and nmr spectroscopy and by elemental analysis.

The olefin 3 was without any further purification subjected to the conditions of the Kakis reaction,⁹ which converted it smoothly to 1,2-diphenyl-1-decanone (4).

After purification of the crude product by recrystallization from methanol followed by thin layer chromatography, a 90% yield (76.5% overall) of pure (mp 56.5–57°) ketone 4 was obtained. The identity of



the ketone was established by infrared, ultraviolet, and nmr spectroscopy and by elemental analysis.

The following two steps in the degradation sequence involved the α -bromination¹¹ of 1,2-diphenyl-1-decanone 4 followed by the collidine dehydrobromination¹² of the resulting 1,2-diphenyl-2-bromo-1-decanone (5).

Both reactions were nearly quantitative. The identity of the products was in each case confirmed by infrared and nmr spectroscopy. The ketones 6 and 6' were further identified by elemental analysis.

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As expected, the collidine dehydrobromination of **5** produced a mixture of *cis* (**6**) and *trans* (**6'**) α,β -unsaturated ketones which were separated by thin layer chromatography on fluorescent silica plates and characterized by nmr.¹³ The ratio of *cis* to *trans* product was about 1:1.6.

The reduction of the isomeric ketones **6** and **6'** was accomplished by means of the specialized reagent¹⁴ $\text{AlNa}(\text{OCH}_2\text{CH}_2\text{CH}_3)_2\text{H}_2$, producing the allylic alcohols **7** and **7'**, respectively. After purification by thin layer chromatography a 75% yield of the *cis* (**7**) and a 50% yield of the *trans* (**7'**) alcohol was obtained. Thus the combined yield of alcohols was 62.5% (48% overall, *i.e.*, based on **1**).

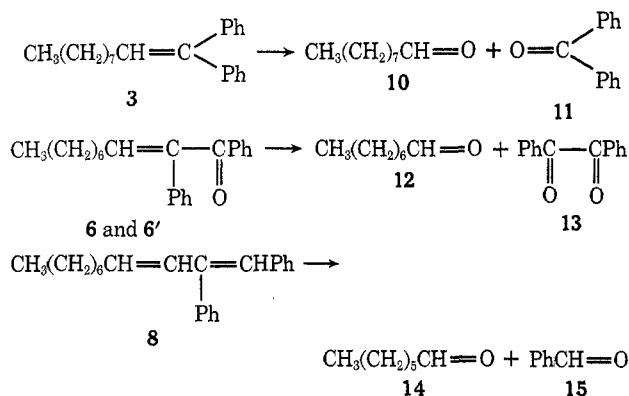
A small quantity (*ca.* 6%) of the ketone **4** was also isolated, presumably stemming from 1,4 reduction of the conjugated ketones **6** and **6'**.

The three components were readily separable by thin layer chromatography.

The alcohols **7** and **7'** were subsequently dehydrated with ethanolic hydrochloric acid.¹⁵ Thus a 70% (34% overall) yield of 1,2-diphenyl-1,3-decadiene (**8**) was obtained whose nmr spectrum was compatible with the *trans,trans* structure shown. In addition a 20% yield of 1,2-diphenyl-3-ethoxy-1-decene (**9**) was isolated. Attempting to minimize the formation of this side product, the dehydration of the alcohols **7** and **7'** was also tried with methanol and isopropyl alcohol solvents. However, the yields were in these cases substantially lower than those obtained from the ethanolic hydrochloric acid dehydration.

Thus it can be seen that the sequence of reactions described above and summarized in Scheme I generates compounds **3**, **6** and **6'**, and **8**, which can in turn be degraded by ozonolysis with the corresponding loss of one, two, and three carbon fragments, respectively. These possibilities are summarized in Scheme II.

SCHEME II



We have in fact carried out the ozonolysis of these compounds by standard procedures¹⁶ and have isolated and identified all the fragments. Thus the ozonolysis of 1,1-diphenyl-1-decene (**3**) resulted in the formation of nonanal (**10**) and benzophenone (**11**). Similarly compounds **6** and **6'** yield octanal (**12**) and

benzil (**13**) and compound **8** yields heptanal (**14**) and benzaldehyde (**15**). To facilitate the separation and identification of the ozonolysis products the mixtures were treated with the Wanzlick reagent,¹⁷ which selectively converts the aldehydes into crystalline derivatives. These derivatives were easily separable by chromatography, and their melting points were in agreement with those reported in the literature.¹⁷ Furthermore, mixture melting points with authentic samples showed no depression. In the case of heptanal and benzaldehyde additional confirmation was obtained by glc and by preparing the 2,4-dinitrophenylhydrazone derivatives. Again the melting points were in agreement with those reported in the literature.

We estimate that the typical ozonolysis yields were about 80%. Thus we have achieved a two-carbon fragment degradation with an overall yield of 60% for the six-step process.

The corresponding overall yield for the removal of three carbon atoms was about 28% for the eight-step process.

The removal of one carbon atom from the chain involves three steps and proceeds with an overall yield of about 70%.

In view of the above, we feel that the procedure we have developed is superior to the existing degradative schemes, not only because of the higher yields but also because in most cases substantial portions of unchanged starting materials can be easily recovered. Thus the process lends itself well to recycling, which may be significant in industrial terms.

From the foregoing discussion, it can be concluded that a useful degradative method has been developed with potential important applications in the chemistry of natural products. This possibility is currently under investigation.

Experimental Section

General.—Melting points were taken on a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Ultraviolet spectra were recorded on a Beckman Model DK2A spectrophotometer. Nmr spectra were determined on a Jeol Model C60H spectrometer using tetramethylsilane as internal standard and are reported in parts per million. Gas chromatographic analysis was carried out on a Loenco Model 160 gas chromatograph equipped with a LAC 446, 8-ft column. Microanalysis were performed by the microanalysis service of C. N. R. S. at the Gif Sur Yvette laboratories in France.

1,1-Diphenyl-1-decanol (2).—The preparation of this compound involved the standard addition of phenylmagnesium bromide (0.5 mol) to a commercial sample¹⁰ of ethyl caprylate (**1**) (10 g, 0.05 mol, 99% pure).

After hydrolysis of the reaction mixture and decomposition with a saturated solution of ammonium chloride, *ca.* 20.3 g of crude product was obtained (yellow oil).

After purification by column chromatography over silica (Merck, 0.05–0.2 mm) using a pentane–ether mixture as the eluent (10:1), 15 g of the pure alcohol (96%) was obtained.

1,1-Diphenyl-1-decene (3).—This compound was prepared by dehydrating a sample of the alcohol **2** (15 g) in refluxing acetic anhydride for a period of 10 hr. After removal of the solvents by rotatory evaporation, the crude product was purified by column chromatography over silica (Merck, 0.05–0.2 mm) using petroleum ether (bp 48–55°) as the eluent. Thus 12.4 g (85%) of pure 1,1-diphenyl-1-decene was obtained. The sample showed the following physical data: ir ($\text{CCl}_2=\text{CCl}_2$) 3080, 3060, 3020, 1600, and 700 cm^{-1} ; nmr (CDCl_3) δ 0.88 (3 H, multiplet,

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methyl), 1.28 (12 H, singlet, $-\text{CH}_3-$), 2.1 (2 H, multiplet, $-\text{CH}_2$ allylic), 6.09 (1 H, triplet, ethylenic, $J = 7.5$ Hz), 7.23 (10 H, aromatic protons).

The above nmr constants were in agreement with those reported in the literature.¹⁸

Anal. Calcd for $\text{C}_{22}\text{H}_{28}$: C, 90.35; H, 9.65. Found: C, 90.37; H, 9.46.

1,2-Diphenyl-1-decanone (4).—A sample (2 g) of the olefin **3** was converted to 1,2-diphenyl-1-decanone (**4**) by the Kakis method.⁹ The crude product (2.4 g) was then purified by recrystallization from methanol, followed by thin layer chromatography of the mother liquors over fluorescent silica using a petroleum ether-ether mixture (6:1) as the eluent. Thus 1.9 g (90%) of pure (mp 56.5–57°) 1,2-diphenyl-1-decanone (**4**) was obtained. Confirmation of structure was obtained by the following physical data: ir (CCl_4) 3090, 3070, 3030, 1690, 1450, and 690 cm^{-1} ; nmr (CDCl_3) δ 0.85 (3 H, multiplet, $-\text{CH}_3$), 1.25 and 2 [14 H, singlet, $(-\text{CH}_2)_8$], 4.53 (1 H, triplet, H α to ketone, $J = 7.5$ Hz), 7.25–8.1 (10 H, aromatic protons); uv (95% EtOH) 244 $\text{m}\mu$ (ϵ 11,180).

Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{O}$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.38; H, 8.98; O, 5.39.

1,2-Diphenyl-2-bromo-1-decanone (5).—A sample (1 g) of the ketone **4** was brominated by the method of Baudry.¹¹ After work-up 1.23 g (99%) of chromatographically pure product was obtained: ir (CCl_4) 3090, 3070, 3030, 1685, 1450, 1225, doublet at 695–685, and 655 cm^{-1} ; nmr (CDCl_3) δ 0.85 (3 H, multiplet, $-\text{CH}_3$), 1.2 [12 H, multiplet, $(-\text{CH}_2)_8$], 2.4 (2 H, multiplet, $-\text{CH}_2\text{CBrPh}$), 7.15–7.85 (10 H, aromatic protons).

cis- and *trans*-1,2-Diphenyl-1-keto-2-decene (**6** and **6'**).—Dehydrobromination of a sample (1.25 g) of compound **5** by collidine⁹ afforded a mixture (0.92 g, 99%) of *cis-* and *trans*-1,2-diphenyl-1-keto-2-decene. Analytical thin layer chromatography of the mixture on silica-silver nitrate (7%) plates with petroleum ether-ether (30:1) eluent showed that it was practically pure.

Separation was achieved on fluorescent silica preparatory plates by multiple elutions with the above solvent mixture (R_f of *trans* compound **6**, R_f of *cis* compound **4**).

Thus 330 mg of the pure *cis* isomer **6** and 530 mg of the pure *trans* isomer **6'** were obtained: ir (CCl_2CCl_2) 3090, 3070, 3030, 1675, 1600, 1450, 1215, and 690 cm^{-1} ; nmr (CDCl_3) for *trans* compound δ 0.85 (3 H, multiplet, $-\text{CH}_3$), 1.25 [10 H, multiplet, $(-\text{CH}_2)_8$], 2.1 (2 H, multiplet, $-\text{CH}_2-$ allylic), 6.28 (1 H, triplet, ethylenic, $J = 7.5$ Hz), 7.25–8.2 (10 H, aromatic protons); for *cis* compound δ 0.87 (3 H, multiplet, $-\text{CH}_3$), 1.27 [10 H, multiplet, $(-\text{CH}_2)_8$], 2.25 (2 H, multiplet, $-\text{CH}_2-$ allylic), 6.5 (1 H, triplet, ethylenic, $J = 7.5$ Hz), 7.2–8 (10 H, aromatic protons); uv (95% EtOH) for *cis* 245 $\text{m}\mu$ (ϵ 18,900); for *trans* 245 $\text{m}\mu$ (ϵ 24,000).

Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{O}$: C, 86.23; H, 8.55; O, 5.22. Found for *cis*: C, 86.28; H, 8.77; O, 5.40. Found for *trans*: C, 86.40; H, 8.52; O, 5.45.

1,2-Diphenyl-2-decen-1-ol (7 and 7'). A. Reduction of Compound 6.—A sample of compound **6** (250 mg) was reduced with bis(2-methoxyethoxy)sodium aluminum hydride, $\text{AlNa}(\text{OCH}_2\text{OCH}_2\text{CH}_3)_2\text{H}_2$, by a procedure similar to that of Bazant, *et al.*¹⁴ On work-up 250 mg of crude product was obtained. Separation was achieved by thin layer chromatography on fluorescent silica plates with a petroleum ether-ether mixture (5:1) as the eluent. Thus 190 mg (75%) of the pure alcohol **7** was obtained. The chromatography also afforded 20 mg of ketone **4**. **7** had ir ($\text{CCl}_2=\text{CCl}_2$) 3620, 3080, 3030, 1600, 1490, 1450, and 700 cm^{-1} ; nmr (CDCl_3) δ 0.87 (3 H, multiplet, $-\text{CH}_3$), 1.23 [10 H, $(-\text{CH}_2)_8$], 1.95 (2 H, multiplet, $-\text{CH}_2-$ allylic), 5.45 (1 H, singlet, $-\text{CHOH}$), 5.92 (1 H, triplet, ethylenic H, $J = 7.5$ Hz), 7.1–7.2 (10 H, aromatic protons).

Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{O}$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.68; H, 9.19; O, 5.20.

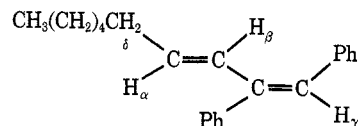
B. Reduction of Compound 6'.—A reduction of a sample (500 mg) of compound **6'** by a procedure identical with the above afforded 440 mg of a crude product. The purification of the product mixture and separation of the components was carried out as before. Thus 250 mg (50%) of alcohol **7'**, 30 mg of ketone **4**, and 20 mg of the dehydration product 1,2-diphenyl-1,3-decadiene (**8**) were obtained in a pure state. **8** had ir same as **7**; nmr (CDCl_3) δ 0.9 (3 H, multiplet, $-\text{CH}_3$), 1.35 [10 H, $(-\text{CH}_2)_8$],

2.25 (3 H, multiplet, allylic $-\text{CH}_2-$ and $-\text{OH}$), 5.88 (2 H, triplet, 6:3:1, $-\text{CHOH}$ and $\text{CH}=\text{C}$), 7.1–7.3 (10 H, aromatic protons).

Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{O}$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.95; H, 9.28; O, 5.14.

1,2-Diphenyl-1,3-decadiene (8).—Dehydration of either alcohol **7** or **7'** (200 mg) by means of ethanolic hydrochloric acid¹⁵ gave after work-up a mixture of two products (200 mg). The mixture was separated on fluorescent silica plates with a mixture of petroleum ether-ether (20:1) as the eluent.

Thus 130 mg (70%) of pure diene **8** (R_f 9) and 45 mg (20%) of 1,2-diphenyl-3-ethoxy-1-decene (**9**) (R_f 7.5) were obtained. Diene **8** had ir ($\text{CCl}_2=\text{CCl}_2$) 3090, 3070, 3030, 1600, 1490, 1470, 1450, and 700 cm^{-1} ; nmr (CDCl_3) δ 0.88 (3 H, multiplet, $-\text{CH}_3$),



1.3 [8 H, $(-\text{CH}_2)_4$], 2.1 (2 H, multiplet, $-\text{CH}_2-$ allylic), two triplets centered at 5.27 (H α , $J_{\alpha,\delta} = 7.5$, $J_{\alpha,\beta} = 16$ Hz); 6.36 (H β , doublet, $J_{\alpha,\beta} = 16$ Hz), 6.42 (H α , singlet), 6.65–7.5 (10 H, aromatic protons).

Anal. Calcd for $\text{C}_{22}\text{H}_{26}$: C, 90.98; H, 9.02. Found: C, 90.84; H, 9.14.

Compound **9** had ir (CS_2) 3080, 3060, 3030, 1080, 760, and 700 cm^{-1} ; nmr (CDCl_3) δ 0.88 (3 H, multiplet, $-\text{CH}_3$), 1.05–1.7 [12 H, large, $(-\text{CH}_2)_6$ and triplet due to $-\text{CH}_3$ of $\text{CH}_3\text{CH}_2\text{O}-$], quadruplet centered at 3.65 due to $-\text{CH}_2-$ of $-\text{OCH}_2\text{CH}_3$, 3.9 (1 H, $-\text{CHOEt}$), 6.7 (1 H, singlet, $\text{RC}=\text{CH}-$), 7–7.6 (10 H, aromatic protons).

Ozonolysis.—All of the ozonolysis reactions were carried out as follows. The reactants were dissolved in a mixture of methanol and methylene chloride (2:3). The solution was then ozonized until the appearance of a blue color (5–10 min).

Decomposition was accomplished by stirring the product mixture with a solution of potassium iodide in glacial acetic acid.

The mixtures were then extracted with ether and the organic phase was decolorized by washing with a sodium thiosulfate solution and a saturated sodium bicarbonate solution.

The combined ether extracts were then dried over anhydrous magnesium and sodium sulfates.

Removal of the solvents by rotatory evaporation afforded the crude mixtures of the ozonolysis products. In some instance direct chromatographic separation of these products proved difficult. Consequently, the mixtures were treated with freshly prepared Wanzlick reagent,¹⁷ which converted all the aldehyde components of the mixtures to the crystalline dianilinoethane derivatives, easily separable by chromatography. Purification was achieved by recrystallization from methanol.

Thus from the ozonolysis of 1,1-diphenyl-1-decene (**3**), non-anal (**10**) was isolated as the dianilinoethane derivative (mp 54–55°) along with benzophenone (mp 46.5–48°).

Similarly the ozonolysis of 1,2-diphenyl-1-keto-2-decenes (**6** and **6'**) afforded octanal **12** as the dianilinoethane derivative (mp 53.5–54.5°) and benzil **13** (mp 95–96°).

Finally the dianilinoethane derivatives of heptanal (**14**) (mp 77–78°) and benzaldehyde (mp 136–137°) were isolated from the ozonolysis of 1,2-diphenyl-1,3-decanone (**8**).

In all of the above cases the observed melting points were in agreement with those reported in the literature.¹⁷ Confirmation was obtained by mixture melting points with authentic samples.

In the last ozonolysis additional confirmation was obtained by gas chromatography of the original mixture against known standards.

Registry No.—1, 110-38-3; 2, 21236-83-9; 3, 1530-27-4; 4, 38821-25-9; 5, 38821-26-0; 6, 38821-29-3; 6', 38821-30-6; 7, 38896-72-9; 7', 38896-73-0; 8, 38821-31-7; 9, 38821-28-2.

Acknowledgments.—The participation of Dr. Fred-eric J. Kakis in this project was made possible in part through a grant by the Research Corporation. We are grateful for this assistance. We also want to thank The École Polytechnique for the financial assistance given to V. Ignatiadou-Ragoussis.