cylinder was cooled to room temperature and the ammonia was evaporated. The resulting solid was crystallized from methanol, yielding 1.3 g of **4a** (30%): mp 271–274°; ir (Nujol) 3440, 3390, 3360, 3210 (broad), 1670, 1650 cm^{-1}; NMR (Me_2SO) δ 8.10–7.30 (m, 4), 7.80 (s, 1), 7.00 (m, 1), 6.74 (d, 1), 6.54 (s, 1), 6.08 (d, 1), 5.42 (s, 2), 4.10 (m, 1), 3.48 (d, 1).

Anal. Calcd for $C_{15}H_{13}N_2O_2Cl$: C, 62.4; H, 4.5; N, 9.7; Cl, 12.3. Found: C, 62.5; H, 4.4; N, 9.8; Cl, 12.5.

4-(2-Methylamino-5-chlorophenyl)-3,4-dihydro-4-hydroxyisocarbostyril (4b). The reaction was performed as in the previous example (**3b**) and **4b** was isolated in 71% yield: mp 238–240°; ir (Nujol) 3380, 3190 (broad), 1670, 1460 cm^{-1}; NMR (Me_2SO) δ 8.10–7.30 (m, 4), 7.82 (s, 1), 7.15 (m, 1), 6.75 (s, 1), 6.64 (d, 1), 6.02 (q, 1), 5.98 (d, 1), 4.20 (m, 1), 3.46 (d, 1), 2.75 (d, 3).

Anal. Calcd for $C_{16}H_{15}N_2O_2Cl$: C, 63.5; H, 5.0; N, 9.3; Cl, 11.7. Found: C, 63.3; H, 5.3; N, 9.0; Cl, 11.5.

4-(2-Amino-5-chlorophenyl)-3,4-dihydro-4-hydroxy-(2-amino)isocarbostyril (5a). A suspension of 0.4 g of **3a** in 5 ml of anhydrous hydrazine was refluxed for 2.5 hr. The resulting solution was poured onto 150 ml of cold water. The mixture was extracted into ethyl acetate and the organic phase dried over sodium sulfate. The solvent was removed under reduced pressure to yield 300 mg of solid which was successively washed with methylene chloride, methanol, and ether to yield 225 mg of **5a** (50%): mp 266–268°; ir (Nujol) 3440, 3360, 3295 (broad), 1650, 1625, 1465 cm^{-1}; NMR (Me_2SO) δ 8.08 (m, 1), 7.80–7.30 (m, 3), 7.01 (m, 1), 6.74 (d, 1), 6.58 (s, 1), 6.36 (d, 1), 5.26 (s, 2), 5.03 (s, 2), 4.36 (d, 1), 3.42 (d, 1).

Anal. Calcd for $C_{15}H_{14}N_3O_2Cl$: C, 59.3; H, 4.7; N, 13.8; Cl, 11.7. Found: C, 59.0; H, 4.8; N, 14.0; Cl, 11.7.

2-Chloro-5-methyl-5,6-dihydro-11-hydroxy-6-oxomorphanthridine-11-acetic Acid Ethyl Ester (6). To a suspension of 14.0 g (0.215 mol) of zinc (activated, 10 mesh) in 75 ml of benzene was added a solution of 10.0 g (0.06 mol) of ethyl bromoacetate and 11.0 g (0.041 mol) of **1** in 75 ml of benzene. When the reaction started, the mixture was refluxed for 5 hr and then poured onto 400 ml of 20% acetic acid and extracted with ethyl acetate. The organic phase was washed twice with water and dried over sodium sulfate. The solvent was removed under reduced pressure to yield 10.4 g of **6** (72%): mp 151–154°, recrystallization from ether raised the melting point to 162–165°; ir ($CHCl_3$) 3450 (broad), 1705, 1630 cm^{-1}; NMR ($CDCl_3$) δ 8.10–7.10 (m, 7), 5.46 (s, 1), 4.04 (q, 2), 3.64 (s, 3), 3.26 (d, 1), 3.02 (d, 1), 1.04 (t, 3).

Anal. Calcd for $C_{19}H_{18}NO_4Cl$: C, 63.4; H, 5.0; N, 3.9; Cl, 9.9. Found: C, 63.5; H, 4.9; N, 3.8; Cl, 10.3.

6′-Chloro-1′-methylspiro[phthalan-1,4′(3*H*)-quinoline]-2′,3(1′*H*)-dione (7). Twelve grams of **6** was heated at 140°. The temperature was then raised to 180° over a period of 20 min and kept there for 1 hr, during which time the material was constantly stirred. The resulting solid was extracted in a Soxhlet apparatus using ether as the solvent. After 5 days, the ether was removed under reduced pressure to afford a solid which was crystallized from methylene chloride–ether to yield 5.0 g of **7** (47%): mp 234–235°; ir ($CHCl_3$) 1775, 1680 cm^{-1}; NMR ($CDCl_3$ + Me_2SO) δ 8.20–7.50 (m, 4), 7.40 (m, 1), 7.10 (d, 1), 6.75 (d, 1), 3.48 (s, 3), 3.16 (s, 2).

Anal. Calcd for $C_{17}H_{12}NO_3Cl$: C, 65.1; H, 3.9; N, 4.5. Found: C, 65.2; H, 3.8; N, 4.5.

6-Chloro-1-methyl-4-(2-carboxyphenyl)carbostyril Hydrazine Salt (8). A mixture of 1.0 g of **6** and 0.5 ml of anhydrous hydrazine in 10 ml of ethanol was refluxed for 4 hr. The solvent was removed under reduced pressure and the resulting foam was dissolved in 25 ml of methylene chloride. After the solution is formed, immediate crystallization occurs yielding 0.65 g of **8** (68%): the material has no definite melting point; ir (KBr) 1640 (broad), 1580 cm^{-1} (broad); NMR (Me_2SO) δ 8.20–7.00 (m, 12), 6.42 (s, 1), 3.68 (s, 3).

Anal. Calcd for $C_{17}H_{16}N_3O_3Cl$: C, 59.0; H, 4.7; N, 12.2. Found: C, 58.8; H, 4.6; N, 11.9.

The free acid of **8** was isolated by dissolving the hydrazine salt in 2 *N* sodium hydroxide followed by acidification with 2 *N* hydrochloric acid: mp >300°; ir (KBr) 1710, 1635, 1570 cm^{-1}; NMR (Me_2SO) δ 8.05 (m, 1), 7.76 (m, 4), 7.44 (m, 1), 6.96 (m, 1), 6.51 (s, 1), 3.69 (s, 3), exchangeable acid proton falls in with the water peak of the solvent.

Anal. Calcd for $C_{17}H_{12}NO_3Cl$: C, 65.2 ; H, 3.8; N, 4.5. Found: C, 65.0; H, 4.2; N, 4.3.

The values for the *N*-methyl protons and the proton in the 3 position of **9** were δ 3.68 and 6.49, respectively. These chemical shifts were in close accord with those of the free acid of **8** (see above).

Acknowledgment. The authors wish to thank Dr. Sandor Barcza and his associates for ir and NMR spectra, Mr. Robert Clark for mass spectra, and Dr. Renate Coombs for interpreting the mass spectra.

Registry No.—**1**, 16219-18-4; **3a**, 56761-60-5; **3b**, 56761-61-6; **4a**, 56761-62-7; **4b**, 56761-63-8; **5a**, 56761-64-9; **6**, 56761-65-0; **7**, 56761-66-1; **8**, 56761-68-3; **8** free acid, 56761-67-2; 2-chloromorphanthridine-6,11(5*H*)-dione, 786-87-8; ethyl bromoacetate, 105-36-2; hydrazine, 302-01-2.

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Preparation of Diketoheptadecanolides and Cyclohexadecanediones by Thermolysis of a Cyclic Diperoxide

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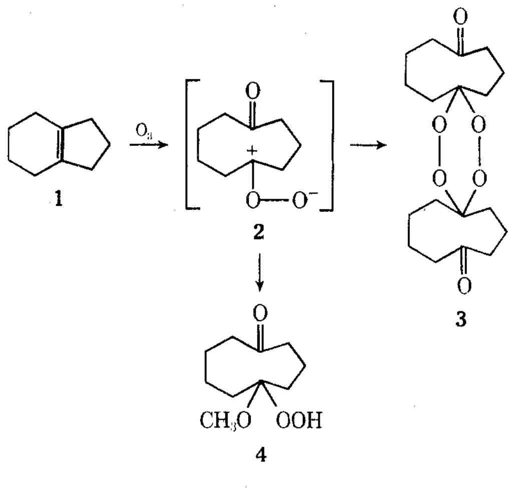
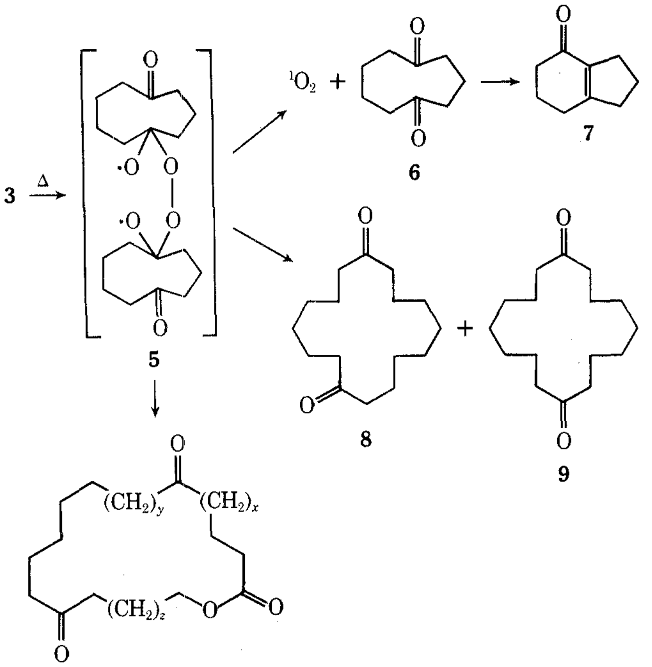
We wish to report the first preparation of four diketoheptadecanolides (**10**). Two known cyclohexadecanediones (**8** and **9**) are also obtained as products of the reaction employed. The method involves the thermolysis of the cyclic diperoxide **3** which is prepared by the reaction of **1** with ozone. The preparation of the diperoxide **3** will first be outlined and then the thermolysis reaction to yield the large-ring products will be discussed.

Scheme I



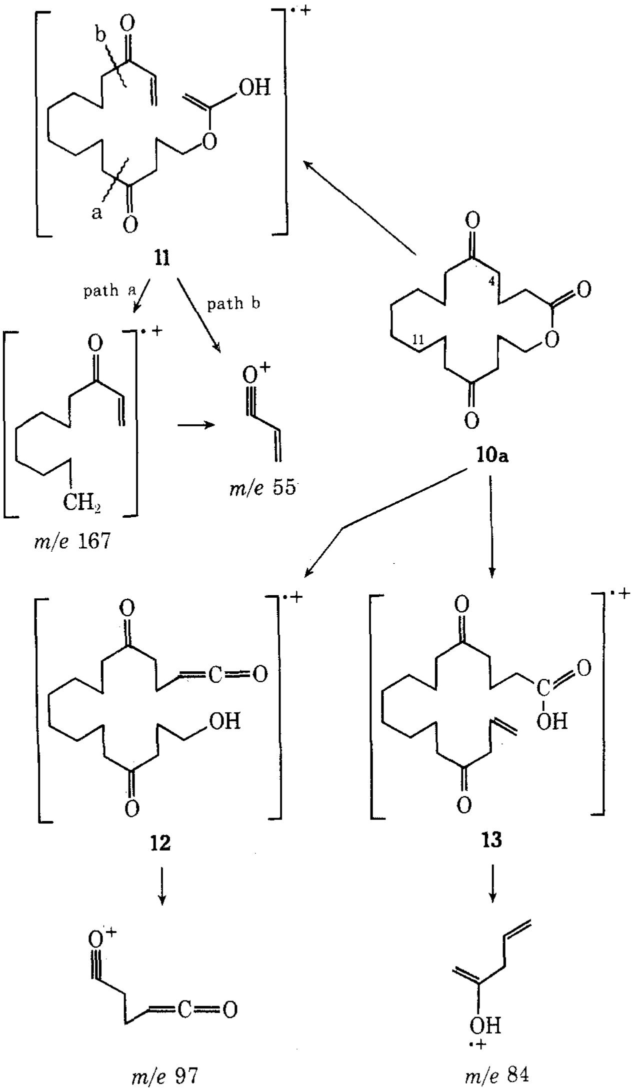
Criegee first reported[1] the isolation of a solid (<10% yield) upon ozonolysis of 4,5,6,7-tetrahydroindan (**1**) in petroleum ether and proposed that this compound was the cyclic diperoxide **3**, formed by dimerization of the intermediate Criegee zwitterion **2**[2] (Scheme I). In a previous paper[3] we reported that ozonolysis of **1** in methylene chloride gave, in addition to the expected diketone **6**, a 17% yield of **3**. This product was not formed when the ozonolysis reaction was conducted in methanol, as **2** was converted to the hydroperoxide **4** before it had an opportunity to dimerize. Although our analytical data for diperoxide **3** differ somewhat from that reported by Criegee,[1] our spectral data (ir, NMR, and mass[4]) and molecular weight determination (see

Scheme II



10a, $x = 1$; $y = 3$; $z = 1$
b, $x = 1$; $y = 2$; $z = 2$
c, $x = 2$; $y = 2$; $z = 1$
d, $x = 2$; $y = 1$; $z = 2$

Scheme III



Experimental Section) are entirely consistent with the structure proposed. Criegee also reported[2] the formation of a cyclic diperoxide upon ozonolysis of 9,10-octalin and Overton[5] isolated the same type of compound upon ozonolysis of β-pinene.

Story reported[6] that thermolysis of dicyclohexylidene diperoxide yielded cyclodecane, undecalactone, and cyclohexanone. Later, he published a review[7] on the thermolysis of related di- and triperoxides as well as kinetic studies[8-10] on the decomposition of these compounds. We wish to report that thermolysis of diperoxide **3** in refluxing decane (174°) yielded three types of products: (i) 1,5-cyclononanedione (**6**), which was isolated as the cyclized product,[3] bicyclo[4.3.0]-1(6)-nonen-2-one (**7**, 18%), (ii) 1,8- (**8**) and 1,9-cyclohexadecanediones (**9**, 50%), and (iii) four diketoheptadecanolides (**10**, 16%) (Scheme II).

The formation of these three types of products may be explained in the following way. Homolysis of an oxygen–oxygen bond in **3** gives **5** which after a double β-scission[6] yields dione **6** and a molecule of singlet oxygen.[8] Loss of two molecules of carbon dioxide from **5** and recombination of the resulting radicals[6] gives diones **8** and **9**. Both of these diones have been prepared[11] previously by another method and comparison of the spectral properties, particularly the mass spectra, confirmed the identity of these compounds. The diones, which are formed in equal amounts, are the major products of the thermolysis reaction and as they may be separated by GC this is an alternative method[11] for the preparation of either **8** or **9**.

Finally, rearrangement of diradical **5** to the three possible acyl peroxides followed by loss of a molecule of carbon dioxide[6,9] leads to the four possible macrolides (**10**). Using a polar silicone phase (OV-210) for the GC separation, it was possible to isolate **10a** and **10d** as crystalline solids while the other two, **10b** and **10c**, were not resolved. The structures proposed for these macrolides are supported by microanalysis, ir, and mass spectrometry, with the latter being most useful for differentiating the isomers. Mass spectrometry has previously been shown[12,13] to be of considerable value in elucidating the structures of naturally occurring macrolides. In the present case, the major peaks in the mass spectrum of **10a** were *m/e* 167, 97, 84, and 55. Scheme III outlines a possible mode of formation of each of these peaks. McLafferty rearrangement of the parent ion of **10a** by transfer of a C-4 hydrogen atom yields **11**, which upon α-cleavage (path a or b) yields either ion *m/e* 167 or *m/e* 55, respectively. Formation of ketene **12**[14] followed by α-cleavage gives fragment *m/e* 97 and formation of carboxylic acid **13**[13] followed by a McLafferty rearrangement involving transfer of a C-11 hydrogen atom yields ion *m/e* 84. Similar fragmentation patterns account for the mass spectra of **10d** as well as the mixture of **10b** and **10c**. The $M^+ - H_2O$ (*m/e* 278) ion is a significant peak in the spectra of all these macrolides and the same peak has been reported previously in the mass spectra of large-ring lactones.[15]

Many macrolides are known to possess antibiotic activity[16] and several approaches to the synthesis of these structures have been reported.[17] Conformational aspects of these compounds have also received attention.[18] In this report we have outlined the facile synthesis of a number of diketoheptadecanolides[19] by an approach which should be suitable to the preparation of other diketomacrolides of different ring sizes.

Experimental Section[20]

Preparation of 10,11,21,22-tetraoxadispiro[8.2.8.2]docosane-4,16-dione (3). A solution of 10.0 g (81 mmol) of 4,5,6,7-tetrahydroindan (1)[21] in 50 ml of methylene chloride was stirred rapidly at −70° while a stream of ozone from a Welsbach generator (200 W) was bubbled through the solution for 45 min. An aqueous solution of 5 g of potassium iodide was added and the reaction mixture was allowed to warm to room temperature The iodine color was discharged with an aqueous solution of sodium thiosulfate and the organic phase was separated, washed with water, and dried ($MgSO_4$). The methylene chloride was removed and ethanol was added to precipitate 2.34 g (17%) of a white solid (**3**), which was recrystallized from ethanol: mp 186–187°; ir ($CHCl_3$) 1700, 1470, 1450, 1075 cm^{-1}; NMR ($CDCl_3$) τ 7.3–7.6 (8 H, m), 7.8–8.5 (20 H, m); mass spectrum *m/e* (rel intensity) 154 (14), 126 (40), 112 (46), 98 (89), 55 (100); mol wt (osmometric) calcd 340, found 347.

Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.47; H, 8.48.

Thermolysis of 3. A sample of 0.30 g (0.88 mmol) of diperoxide **3** was added in portions to 3 ml of refluxing *n*-decane and the resultant solution was refluxed for 1.5 hr. The cooled reaction solution was chromatographed on silica gel (60–200 mesh) using pentane to elute the *n*-decane and 3% ethyl acetate–chloroform to elute the 0.22 g of thermolysis products. GC analysis (190–270°) of these products indicated 18% of **7**, 50% of diones **8** and **9**, 16% of macrolides **10**, and smaller amounts of several other components.

Identification of Thermolysis Products from 3. A. Product **7**, the first major GC peak, was collected and found to be identical with a sample of bicyclo[4.3.0]-1(6)-nonen-2-one prepared previously.[3]

B. Compounds **8** and **9** analyzed as two partially resolved GC peaks of equal area. The first peak was collected, recrystallized from petroleum ether (bp 60–80°), and shown to be 1,8-cyclohexadecanedione (**8**) on the basis of the following data and comparison of this data with that published previously:[11] mp 68–69°; ir (CCl_4) 2940, 2870, 1712, 1460, 1370, 1125 cm^{-1}; mass spectrum *m/e* (rel intensity) 252 (M^+, 14), 234 (13), 195 (21), 140 (17), 125 (18), 112 (37), 97 (41), 84 (74), 55 (100). Similarly, the second peak of the doublet was collected, recrystallized from petroleum ether, and shown to be 1,9-cyclohexadecanedione (**9**) by comparison of the following data with that published previously:[11] mp 80–81° (lit.[11] 78–79°); ir (CCl_4) 2940, 2870, 1719, 1465, 1370, 1115, 1025 cm^{-1}; mass spectrum *m/e* (rel intensity) 252 (M^+, 23), 195 (13), 169 (14), 126 (46), 111 (30), 98 (88), 83 (56), 55 (100).

C. The lactones **10** upon GC analysis (266°) showed three peaks in a ratio of 1:2:1. These peaks were collected by preparative GC and the following data were found for each peak (in order of GC elution). **5,14-Diketoheptadecanolide (10a):** mp 50.5–51.0° (recrystallized as plates from petroleum ether, bp 60–80°); ir (CCl_4) 2930, 2855, 1736, 1716, 1158, 1128 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 14), 278 (19), 167 (56), 97 (100), 84 (86), 55 (62).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.73; H, 9.46.

Mixture of 5,13-Diketoheptadecanolide (10b) and 6,14-Diketoheptadecanolide (10c). This GC fraction was an oil: ir (CCl_4) 2930, 2860, 1734, 1714, 1160 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 12), 278 (9), 167 (19), 153 (28), 111 (56), 98 (80), 97 (65), 84 (61), 55 (100). **6,13-Diketoheptadecanolide (10d).** This last GC peak was recrystallized from petroleum ether (bp 60–80°): mp 59.0–59.5°; ir (CCl_4) 2935, 2860, 1738, 1718, 1135 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 7), 278 (8), 153 (33), 111 (70), 98 (100), 55 (90).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.85; H, 9.75.

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Registry No.—1, 695-90-9; 3, 56678-87-6; 7, 22118-01-0; 8, 17853-46-2; 9, 31067-25-1; **10a,** 56678-88-7; **10b,** 56678-89-8; **10c,** 56678-90-1; **10d,** 56678-91-2; ozone, 10028-15-6.

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The Pyridine Route to α-Substituted Cyclohexenones

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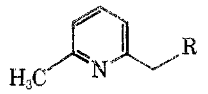
In the pyridine route to steroids,[1,2] it has been shown that 6-substituted α-picolines (**1**) may be converted to 3-substituted cyclohexenones of the type **3**. Fortunately, in the most relevant cases (i.e., where R represents a cycloalkanone ketal substituted at its α position), the 2,6-diketone intermediate **2** suffers aldolization to give **3** rather than its isomer, **4**. System **4** is, in fact, the predominant product



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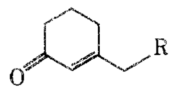

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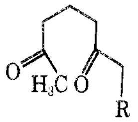

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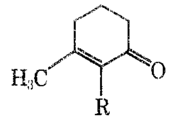

4

where R in diketone **2** represents a straight-chain alkyl group.[3,4] The structural factors which are decisive in promoting one mode of cyclization over the other are being investigated.[5] The issue of isomeric possibilities in the aldolization process does not arise for 4-acylbutyraldehydes (**6**). Such systems should be derived by reductive hydrolysis of 2-substituted pyridines (**5**). Below are described some ap-