Structure Determination of Cyclopropane-Substituted Acids by Mass Spectrometry

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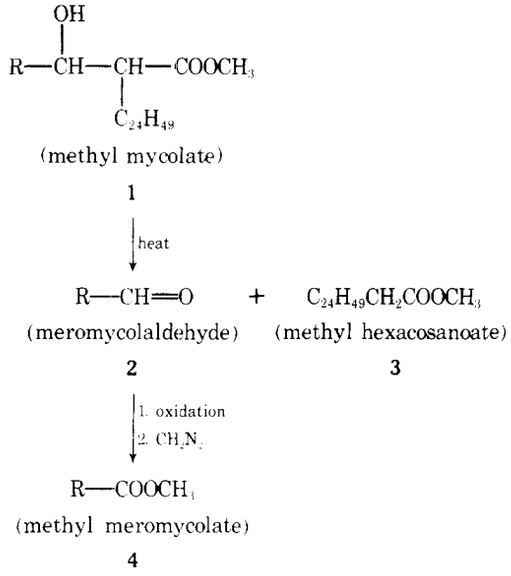
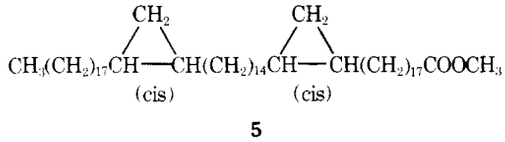
Calibration information has been obtained that will be useful in mass spectral studies of bis cyclopropane meromycolic compounds derived from mycobacterial mycolic acids. The compounds examined include a synthetic meromycolic ester, its monoketo derivatives, and its pyrrolidide. Methyl *cis*-9,10-methyleneoctadecanoate and its derivatives were also examined. The study shows that the monoketo compounds are to be preferred.

The mycolic acids, isolated from tuberculosis bacteria, are high molecular weight β-hydroxycarboxylic acids carrying a tetracosanyl (or docosanyl) group on the α position.[1,2] In the many inquiries into the nature of these compounds, pyrolysis of the methyl esters **1** to the corresponding meromycolaldehydes (**2**) plus methyl hexacosanoate (**3**) has been a standard procedure. Nuclear magnetic resonance and infrared absorption data for the corresponding meromycolate esters **4** as well as for the parent mycolates **1**, and, even more important, their mass fragmentation patterns, have provided much of the detailed structural information. The mass spectral studies, however, have invariably been complicated by the fact that the materials examined, instead of single pure compounds, have been groups of functionally and structurally related molecules.[2b] Another serious handicap has been the absence of appropriate model compounds. As a result there has been a certain degree of uncertainty—sometimes disagreement—in the structural assignments.[3]



We have recently completed a total synthesis of a representative methyl meromycolate (**5**) of the type containing cis-disubstituted cyclopropane rings.[4] The availability of this compound made it possible for the first time to provide a reliable reference standard. With this purpose in mind we determined the fragmentation pattern of the synthetic ester **5**



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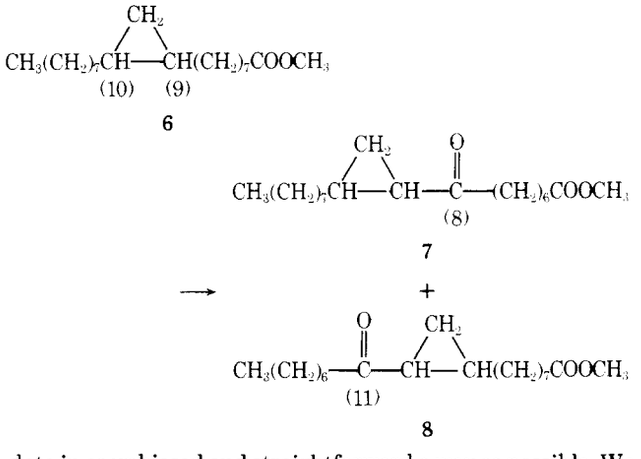
as well as of two promising derivatives, the monoketo esters and the meromycolic pyrrolidide. To obtain further pertinent data, we also examined a related cyclopropane compound, methyl *cis*-9,10-methyleneoctadecanoate. The present paper reports our results.

Methyl *cis*-9,10-Methyleneoctadecanoate (6). Methyl *cis*-9,10-methyleneoctadecanoate, taken as a reasonable starting point for modeling the more complex bis cyclopropane ester **5**, gave a mass spectrum that was not particularly useful for locating the cyclopropane ring.[5-13] We then turned to two methods for modifying cyclopropane compounds, which we hoped would make the mass spectra more informative.[8,11,12,14-16]

Monoketo Derivatives 7 and 8 of Methyl *cis*-9,10-Methyleneoctadecanoate. Promé reported that the chromium(VI) oxidation of cyclopropanes fused on a straight chain converts the alkyl methylene group next to the three-membered ring to an oxo group.[15,17] He also showed[8] that the tendency for mass spectral cleavage on either side of the carbonyl group[18] carries over to the cyclopropyl ketones. With methyl *cis*-9,10-methyleneoctadecanoate (**6**) as the starting point, the 8-keto and the 11-keto derivatives **7** and **8** were obtained as products. In analyzing the mass spectra we sought to use the data in as unbiased and straightforward a way as possible. We simply ordered the peaks according to relative abundance and then, relying only on the prominent peaks, proceeded to relate *m/e* values to structural features.



The fragmentation pattern of the 8-keto derivative **7** shows an intense and obvious molecular peak at M 324 (rel intensity 28). The base peak at *m/e* 171 (100), which can be associated with preferred cleavage α to the keto group, is alone enough to locate the three-membered ring on the chain at the 9,10 position. The prominent companion peak at *m/e* 181 (29% and ninth in abundance order) corresponding to cleavage on the other side of the keto group, supports the assignment. Other high-intensity peaks, although all confirmatory according to Promé's interpertations,[8] are less straightforward and, so far as locating the ring is concerned, are redundant.

In the mass spectrum of the 11-keto derivative **8**, the most intense peak at *m/e* 127 (100), corresponding to one of the

α-keto cleavages, again immediately and correctly positions the three-membered ring at 9,10. The other α-keto cleavage (*m/e* 225, rel intensity 4) does not stand out and therefore is not used for the assignment. The peak at *m/e* 324 (17), appearing seventh in the order of relative intensity, is unmistakably the molecular peak.

Clearly the mass spectral data from the two monoketone derivatives of cyclopropane ester **6** convincingly bracket the ring at the 9,10 position.

Pyrrolidide 9 of *cis*-9,10-Methyleneoctadecanoic Acid. In their search for a derivative of unsaturated straight-chain acids whose mass spectra would help to locate the double bonds, Vetter et al.[19] found that the acyl pyrrolidides showed considerable promise. Holmann and his colleagues[16,20,21] extended and consolidated this observation, and also suggested that mass spectral data from the pyrrolidides of cyclopropane fatty acid could help to determine the position of the three-membered ring along the chain. To check this possibility, we investigated the fragmentation pattern of *cis*-9,10-methyleneoctadecanoic pyrrolidide (**9**). As before, the approach was to seek information only from the abundant peaks.

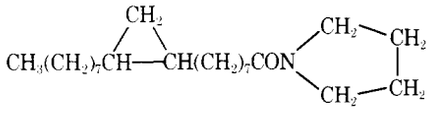


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Table I, which lists the first dozen peaks according to their intensity, identifies the McLafferty cleavage fragment (*m/e* 113) as the most abundant by far. The molecular mass peak at *m/e* 349 and the isotope (M + 1) peak at 350 are also prominent. Beginning with *m/e* 98, a series of peaks appear that correspond to $(CH_2)_nCONC_4H_8$ as well as to this fragment plus or minus protons. The prominent peak at 182 (n = 6) requires a minimum of six methylene groups extending from the amide carbonyl toward the cyclopropane ring. The next higher homologue (n = 7, *m/e* 196) is about half as intense and is not included in Table I. These data, although not fixing the ring, suggest correctly that it is located at or beyond the 8,9 position of **9**.

The higher mass region of the fragmentation pattern includes peaks for the series $(CH_2)_n(C_3H_4)CONC_4H_8$, the first two members of which (*m/e* 236 and 250 for n = 0 and 1) are sufficiently intense to be listed in Table I. The *m/e* 250 peak, corresponding to a cyclopropylmethyl system, emerges as the most prominent peak of this homologous series. If further work with other model pyrrolidides supports the tentative conclusion that such cyclopropylmethyl cleavage is preferred, this peak alone would suffice to locate the ring.

Test was made of an adaptation of the rule developed originally[20] for locating olefinic double bonds. The rule depends on noting where the maxima between *m/e* signal clusters are separated by 12 instead of the more usual 14 mass units. Inspection of the mass spectrum of pyrrolidide **9** shows that the significant interval comes between *m/e* 196 and 208. If the *m/e* 196 peak is identified with the fragment terminating at position 8 ($C_{12}H_{12}NO$) and the *m/e* 208 peak is identified with the fragment terminating at position 9 ($C_{13}H_{24}NO$ minus 2 H), the extended rule[20] would place the cyclopropane ring at the 9,10 position, where in fact it is. This adaptation treats the cyclopropane ring as if it were simply a double bond at the point of ring fusion. How reliable this approach will prove to be must await further work with other model pyrrolidides.

In summary, the mass spectrum of the parent methyl *cis*-9,10-methyleneoctadecanoate (**6**) gives no simple and uncomplicated structural information. On the other hand, the easily derived cyclopropyl keto esters produce data that locate the ring in a straightforward manner. While the pyrrolidide appears promising, further investigation is called for.

Table I. Prominent Peaks in the Mass Spectrum of *cis*-9,10-Methyleneoctadecanoic Pyrrolidide (9)[a]

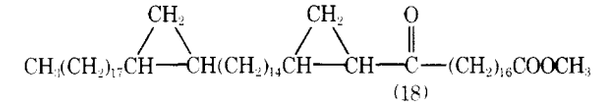
m/e	Rel intensity	Assignment: Formula	Assignment: Parent structural feature
113	648	$C_6H_{11}NO$	$CH_2CONC_4H_8$ plus H
126	460	$C_7H_{12}NO$	$(CH_2)_2CONC_4H_8$
M 349	230	$C_{23}H_{43}NO$	**9**
98	145	C_5H_8NO	$CONC_4H_8$
250	100	$C_{16}H_{28}NO$	$CH_2(C_3H_4)(CH_2)_7$-$CONC_4H_8$
114	93	$C_{16}H_{12}NO$	$CH_2CONC_4H_8$ plus 2H
127	89	$C_7H_{13}NO$	$(CH_2)_2CONC_4H_8$ plus H
168	70	$C_{10}H_{18}NO$	$(CH_2)_5CONC_4H_8$
236	63	$C_{15}H_{26}NO$	$(C_3H_8)(CH_2)_7CONC_4H_8$
350	62	$C_{23}H_{43}NO$[b]	(M + 1) isotope peak[b]
140	52	$C_8H_{14}NO$	$(CH_2)_3CONC_4H_8$
182	47	$C_{11}H_{20}NO$	$(CH_2)_6CONC_4H_8$
279	34	$C_{19}H_{35}O$	$CH_3(CH_2)_7(C_3H_4)$-$(CH_2)_7CO$

[a] Includes peaks from *m/e* 90 to 360. [b] Calcd (M + 1)/M for $C_{23}H_{43}NO$: 0.26. Found: 0.27.

Synthetic Methyl Meromycolate (5). The next stage was to evaluate mass spectral approaches in locating the cyclopropane rings in the methyl meromycolate (**5**) of known structure.

The mass spectrum of this ester shows that the most abundant peak in the *m/e* 220 to 850 region is the molecular peak at *m/e* 826 (100). The (M + 1) and even the (M + 2) peaks are also high as can be expected from a C_{51} compound. The intense peak at *m/e* 74 (rel intensity 326) for the McLafferty cleavage fragment demands an unsubstituted methylene group next to the ester carbonyl. But aside from these features, the fragmentation pattern appears not to serve in any straightforward way in determining structure, or, more to the point, in locating the two cyclopropane rings.

Monoketones from Synthetic Methyl Meromycolate. Chromium(VI) trioxide oxidation of meromycolate **5** furnished the expected cyclopropyl ketones **10–13**, which were



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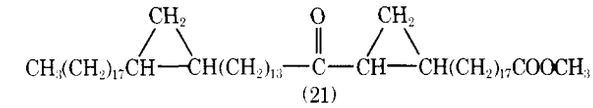

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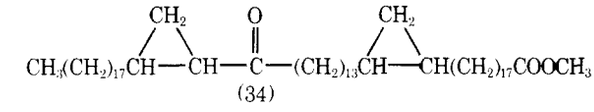

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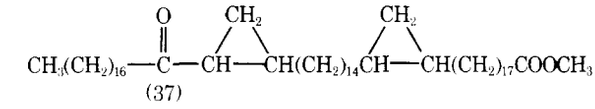

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isolated and examined as a mixture of the four compounds. If their fragmentation pattern could serve in an uncomplicated manner to locate the keto groups, the structure of the carbon skeleton would follow automatically. As with the simpler monoketo derivatives of methyl *cis*-9,10-methyleneoctade-

Table II. Prominent Peaks in the Mass Spectrum of Monoketo Esters 10–13[a]

m/e	Rel intensity	Assignment: Formula	Assignment: Parent structural feature
M 840	185	$C_{57}H_{108}O_3$	**10, 11, 12, 13**
841	110	$C_{57}H_{108}O_3$	(M + 1) isotope peak[b]
557	100	$C_{39}H_{73}O$	$CH_3(CH_2)_{17}(C_3H_4)$-$(CH_2)_{14}(C_3H_4)CO$
842	80		
326	65	$C_{20}H_{38}O_3$	$CHCO(CH_2)_{16}COOCH_3$ plus 2 H
558	55	*c*	*c*
601	55	$C_{40}H_{73}O_3$	$CO(C_3H_4)(CH_2)_{14}(C_3H_4)$-$(CH_2)_{17}COOCH_3$
808	47	$C_{56}H_{104}O_2$	M minus CH_4O
809	45	$C_{56}H_{105}O_2$	M minus CH_3O
311	42	$C_{19}H_{35}O_3$	$CO(CH_2)_{16}COOCH_3$
602	36	*d*	*d*
267	34	$C_{18}H_{35}O$	$CH_3(CH_2)_{16}CO$

[a] Includes peaks from *m/e* 150 to 850. [b] Calcd (M + 1)/M for $C_{57}H_{108}O_3$: 0.63. Found: 0.59. [c] This is a composite peak due in part to the isotopic $C_{39}H_{73}O$ fragments from *m/e* 557. Calcd (M + 1)/M for $C_{39}H_{73}O$: 0.43. Found: 0.55. [d] A composite peak due in part to isotopic $C_{40}H_{73}O_3$ fragments (nominal *m/e* 601). Calcd (M + 1)/M for $C_{40}H_{73}O_3$: 0.45. Found: 0.65.

canoate, we sought for relationships between the mass numbers of prominent peaks and recognized modes of cleavage.

Table II shows that the most abundant fragment in the *m/e* 150 to 850 sweep comes at *m/e* 840 and corresponds to the molecular mass of the keto esters **10–13.** The high peaks at *m/e* 557 and 311 (respectively third and tenth in intensity) neatly match the fragments arising from cleavage on either side of the 18-keto group in keto ester **10.** The related peaks at *m/e* 503 (rel intensity 29) and 365 (16) for the 21-keto group in **11** appear in the mass spectrum, but they fail to stand out and thus do not meet our criterion of usefulness. However, these peaks are not needed, since either of the abundant fragments from the 18-keto compound is alone enough to establish the presence of a fused cyclopropane ring at the 19,20 position.

So far as the other ring is concerned, the intense peaks at *m/e* 601 and 267 (seventh and twelfth in intensity) correlate with α-cleavage in the 37-keto derivative **13;** either one fixes the distal cyclopropane ring at the 35,36 position. The fragments from the 34-keto compound **12** (*m/e* 547 with intensity 20, and *m/e* 321 with intensity 31) are not prominent and are not used.

Accordingly, readily identified peaks furnish more than enough information to place the two rings of the bis cyclopropane meromycolate **5** correctly at position 19,20 and 35,36. The analysis and conclusions with this more complicated compound are as direct as with the simpler 9,10-methyleneoctadecanoic ester **6.** None of the remaining peaks of Table II contradicts the structural assignment, and in fact at least one (*m/e* 326) provides further confirmation. The chromium oxidation method may be accepted as reliable and of proved value when applied to related bis cyclopropanes of unknown structures.

Pyrrolidide 14 of Methyl Meromycolate. To round out our calibration data we next examined the fragmentation pattern of pyrrolidide **14.** The most abundant peak by far (cf. Table III) is the molecular peak at *m/e* 865; the isotope peak

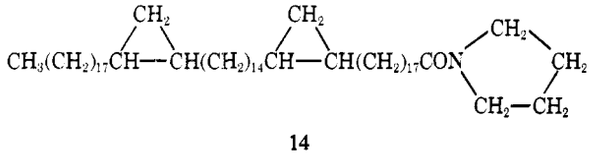

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Table III. Prominent Peaks in the Mass Spectrum of Meromycolic Pyrrolidide 14[a]

m/e	Rel intensity	Assignment: Formula	Assignment: Parent structural feature
M 865	955	$C_{60}H_{115}NO$	**14**
795	760	$C_{56}H_{107}O$	$CH_3(CH_2)_{17}(C_3H_4)(CH_2)_{14}$-$(C_3H_4)(CH_2)_{17}CO$
866	667	$C_{60}H_{115}NO$[b]	(M + 1) isotope peak[b]
796	485	$C_{56}H_{107}O$[c]	*m/e* (795 + 1) isotope peak[c]
867	485		
797	348		
868	227		
864	197	$C_{60}H_{114}NO$	14 minus H
798	150		
168	100	$C_{10}H_8NO$	$(CH_2)_5CONC_4H_8$
577	100	$C_{39}H_{73}O$	$CH_2(C_3H_4)(CH_2)_{14}(C_3H_4)$-$(CH_2)_{17}CO$ plus H
390	94	$C_{26}H_{48}NO$	$CH_2(C_3H_4)(CH_2)_{17}CONC_4H_8$
262	79		Composite
869	78		
853	76		
308	76	$C_{20}H_{38}NO$	$(CH_2)_{15}CONC_4H_8$
350	76		

[a] Includes peaks from *m/e* 150 to 890. [b] Calcd (M + 1)/M for $C_{60}H_{115}NO$: 0.67. Found: 0.69. [c] Calcd (M + 1)/M for $C_{56}H_{107}O$: 0.62. Found: 0.64.

at *m/e* 866 is also correspondingly high. Identification of the fragments contributing to the intense *m/e* 867, 868, and 869 peaks will have to await high-resolution mass spectral studies. The intense peak at *m/e* 795 (also its isotopic peak at *m/e* 796) corresponds to the acylium fraction formed by loss of the entire pyrrolidine section. The fragmentation pattern for the smaller pyrrolidide **9** includes a corresponding acylium fragment, but in much lower relative abundance. In the intermediate mass region, the three most intense peaks come at *m/e* 168, 577, and 390. The *m/e* 390 peak can be matched with a cyclopropylcarbinyl rupture (cf. Table III). Although the cyclopropylcarbinyl fragment containing two rings ($C_{43}H_{80}NO$, *m/e* 626, rel intensity 33) does not stand out,[22] the *m/e* 577 peak (Table III) might serve in its place.

The mass spectrim of pyrrolidide **14** presents a series of peaks at mass values below 200, which can be associated with the fragments $(CH_2)_nCONC_4H_8$, or with this grouping plus or minus a proton, and which gives limiting information about the location of one of the cyclopropane rings. The abundances for those with n = 0, 1, 2, and 3 (*m/e* 97 and 98, 112, 126, and 127, and 140) are all high. After this there is a downward trend, with the peaks for n = 4–10 appearing with intensities 40–100% on the scale of Table III. This series could be interpreted as demonstrating at least ten methylene groups extending back from the amide carbonyl. The exceptionally intense peak at *m/e* 308 (76) could be used to justify extending the chain to n = 15; the correct value of n = 17 is not indicated in any obvious way. A similar argument could be made concerning the chain of CH_2 groups between the two cyclopropane rings, that is, about the fragments $(CH_2)_n(C_3H_4)(CH_2)_{17}CONC_4H_8$. Here, however, a limiting value for n cannot be arrived at in a clear-cut way, so that this kind of data treatment—and for that matter a similar analysis of the peaks on the terminal methyl side of the second ring—appears not particularly rewarding.

In applying the possible extension of the Andersson–Holman rule (see above), an *m/e* 12 increment between adjacent cluster maxima can be found at *m/e* 364 and 376. By the same

analysis as with the lower molecular weight pyrrolidide **9**, this would place the first cyclopropane ring at the 21,22 position, whereas in fact it is at the 19,20 position. In the higher *m/e* region of the mass spectrum, where information about the second cyclopropane ring would be sought, the sequence of cluster maxima is not regular enough to warrant applying the increment approach.

Summary. Mass spectral results with methyl *cis*-9,10-methyleneoctadecanoate (**6**) and with synthetic methyl meromycolate (**5**) as well as with their pyrrolidides and their monoketo derivatives show that while all the compounds are useful for determining molecular weight, only the monoketones serve in a straightforward way in locating the cyclopropane rings. The monoketones may be recommended for structural work with bis cyclopropane acids obtained by degrading the natural products.

In our hands, trial of an adaptation of a device developed originally for fixing the position of olefinic double bonds in pyrrolidides of unsaturated straight-chain acids for the purpose of locating the rings in cyclopropane acids did not give wholly convincing results. In the pyrrolidides tested, whether cleavage to produce cyclopropylcarbinyl fragments will prove to be a generally preferred mode and therefore reliable in providing structural information must await further work with other cyclopropane pyrrolidides.

Experimental Section

General Information. Most of the mass spectra were determined by direct injection into an AEI MS-9 instrument at 70 eV. Some of the determinations, especially of the lower molecular weight compounds, were run with a Hitachi Perkin-Elmer RMU-6L mass spectrometer. Generally, preparative layer chromatography made use of 0.25 mm silica plates (E. Merck) measuring 5 × 20 or 20 × 20 cm. Where isotopic abundance ratios are calculated, the formulas given by Beynon[23] were used.

Methyl *cis*-9,10-Methyleneoctadecanoate (6). Methyl oleate was converted to the desired cyclopropane **6** by taking 3.0 g (10 mmol) of the oleate with 60 g of diiodomethane and 20 g of zinc–copper couple in 150 ml of ether.[9,10,24] To remove the persistent residue of about 15% of unsaturated material (δ 5.3 ppm), the straw-colored oily product (3.0 g) in 100 ml of chloroform was stirred with *m*-chloroperbenzoic acid (0.40 g of 85% reagent or 1.8 mmol) at 25 °C for 3 h. The methyl *cis*-9,10-methyleneoctadecanoate obtained after this treatment showed ir 1745 cm^{-1}; NMR ($CDCl_3$) δ 5.3 (no signal), 3.67 (s, 3 protons, OCH_3), 2.20 (t, J = 8 Hz, 2 H, CH_2CO), 1.20 [broad s, 26 H, $(CH_2)_7$ plus $(CH_2)_6$], 0.90 (t, J = 5 Hz, 3 H, CH_3C), 0.55 (broad s, 3 H, *cis*-cyclopropane H's), −0.35 ppm (m, 1 H, cyclopropane H cis to alkyl groups). Later work showed that the cyclopropane product **6** was quite stable in contact with ozone at low temperature, so that treatment with ozone offers an alternate way of getting rid of unused oleic ester. Calcd for $C_{20}H_{38}O_2$: mol wt, 310. Found: *m/e* 310 (injection port 180 °C).

Cyclopropyl Ketones 7 and 8 from Methyl *cis*-9,10-Methyleneoctadecanoate (6). An oxidation mixture was made up by dissolving 0.41 g of chromium trioxide in 3.3 ml of 1:1 acetic anhydride–acetic acid and diluting with 23.5 ml of carbon tetrachloride. Methyl *cis*-9,10-methyleneoctadecanoate (10 mg) in 0.2 ml of carbon tetrachloride on treatment with 0.84 ml of the oxidation mixture at 0 °C for 2 h furnished the keto products which were separated by preparative layer chromatography. Analytical thin layer chromatography showed single spots with R_f 0.25 for the 8-keto compound **7** and 0.30 for the 11-keto compound **8**.[8]

Calcd for $C_{20}H_{36}O_3$: mol wt, 324. Found for both compounds: *m/e* 324.

Pyrrolidide 9 of *cis*-9,10-Methyleneoctadecanoic Acid. Essentially by following earlier directions,[19,20] 10 mg of methyl *cis*-9,10-methyleneoctadecanate with pyrrolidine and acetic acid furnished pyrrolidide **9** (10 mg) as a faintly yellow oil.

Calcd for $C_{23}H_{43}NO$: mol wt, 349. Found: *m/e* 349.

Monoketo Derivatives (10–13) of Synthetic Methyl Meromycolate (5). The bis cyclopropane methyl meromycolate (2.0 mg) in 0.18 ml of carbon tetrachloride was allowed to stand for 1 h with 0.08 ml of the oxidation mixture. Another 0.05-ml portion was then added, followed after 1.5 h by a third portion. After a total reaction period of 4.5 h, the oxidation mixture was processed as before. Preparative-plate chromatography (silica, benzene solvent) afforded the desired mixture of monoketo esters (**10–13**) as a white solid showing a single spot on analytical thin layer chromatography (R_f 0.55 with benzene on silica).

Pyrrolidide 14 of Synthetic Meromycolic Acid (5). By employing directions essentially the same as these used for methyleneoctadecanoic compound **9**, 1.2 mg of the bis cyclopropane methyl meromycolate (**5**) was warmed with 0.5 ml of pyrrolidine plus 0.05 ml of glacial acetic acid. The crude product was purified on a preparative-layer plate (ether–benzene, 2:3), to give the white solid pyrrolidide **14**.

Calcd for $C_{60}H_{115}NO$: mol wt, 865. Found: *m/e* 865, with only traces of peaks at *m/e* greater than 865.

Acknowledgment. This investigation has been supported by U.S. Public Health Service Grant 09308 from the National Institute of Allergy and Infectious Diseases.

Registry No.—**5**, 59014-67-4; **6**, 3971-54-8; **9**, 60103-87-9; **10**, 60103-88-0; **11**, 60103-89-1; **12**, 60103-90-4; **13**, 60103-91-5; **14**, 60103-92-6; methyl oleate, 112-62-9.

Supplementary Material Available. The full mass spectral line diagrams for all compounds discussed in this paper (8 pages). Ordering information is given on any current masthead page.

References and Notes

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