ml), and methyl iodide (0.3 ml) was added. After standing overnight, the solution was evaporated to small bulk, and ethyl acetate was added when colorless needles of 2-ethyl-3,4,5-trimethoxyphenylethyltrimethylammonium iodide (**11**) separated (84 mg), mp 216–218°. Fine needles, mp 218–219°, were obtained on recrystallization from ethanol. *Anal.* Calcd for $C_{16}H_{28}O_3NI$: C, 46.95; H, 6.89; N, 3.42. Found: C, 46.81; H, 6.67; N, 3.40.

The mother liquor from which the methiodide **8** had separated was treated with ether when a product, mp 150–170°, separated. On attempted crystallization from a mixture of ethanol and ethyl acetate a product, mp 266–267°, was obtained. This material was identical (infrared, mixture melting point) with trimethylamine hydriodide. *Anal.* Calcd for $C_3H_{10}NI$: C, 19.26; H, 5.39; N, 7.48. Found: C, 19.53; H, 5.50 N, 7.27.

(C) Hofmann Degradation of the Methiodide 11. The methiodide **11** (80 mg) was subjected to a Hofmann degradation using the same procedure as that described for the degradation of N,N-dimethylmescaline methiodide. The 2-ethyl-3,4,5-trimethoxystyrene (**14**) was hydroxylated with osmium tetroxide and cleaved with sodium metaperiodate. The resultant 2-ethyl-3,4,5-trimethoxybenzaldehyde is a liquid at room temperature and was extracted from the periodate solution with ether. The evaporated ether extract was shaken with a solution of hydroxylamine hydrochloride (200 mg) in 2 ml of 10% aqueous sodium carbonate solution. The mixture was extracted with ether. The dried ether extract was evaporated, and the residue was distilled (180°, 0.1 mm). The viscous distillate solidified on standing and was crystallized from petroleum ether (bp 60–70°) affording colorless needles of 2-ethyl-3,4,5-trimethoxybenzaldoxime (26 mg), mp 64–65°. *Anal.* Calcd for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.95; H, 7.20; N, 5.95.

O,N-Dimethyl-DL-anhalonidine Methiodide-9-C.[14] Mescaline sulfate (5 g), hydrated sodium acetate (4 g), sodium acetate-2-C^{14} (1.0 mg, 0.05 mcurie), and 1-ethyl-3(3-dimethylaminopropyl)carbodiimide hydrochloride (20 g) were dissolved in water (30 ml), and the mixture was shaken at room temperature for 18 hr. The solution was made acidic by the addition of hydrochloric acid and then extracted with benzene. The dried benzene extract was evaporated and the residue crystallized from a mixture of benzene and petroleum ether yielding colorless plates of N-acetyl(2-C^{14})mescaline (3.5 g), mp 91–92° (lit.[17] mp 93–94°), having a specific activity of 5.85×10^6 dpm/mmole. The N-acetylmescaline (3.5 g) was dissolved in toluene (50 ml), and phosphorus pentoxide (7 g) was added. The mixture was refluxed for 30 min, cooled, and added to ice. The mixture was made basic with sodium hydroxide and extracted with ether. The residue obtained on evaporation of the dried ether extract was dissolved in absolute ethanol (20 ml), and sodium borohydride (1 g) was added. After refluxing for 10 min, the solution was allowed to cool for 1 hr. The mixture was evaporated to dryness, 1% sodium hydroxide added to the residue, and O-methyl-DL-anhalonidine extracted with ether. This base was converted to O,N-dimethyl-DL-anhalonidine methiodide-9-C^{14} by refluxing in ethanol with methyl iodide (3.0 ml) in the presence of sodium bicarbonate (3.0 g). The methiodide (4.6 g), mp 231–232°, was isolated as previously described and had an activity of 5.65×10^6 dpm/mmole.

The activities of the degradation products of this synthetic material and of the alkaloids isolated from peyote are recorded in Table I.

Acknowledgment. The author thanks Mr. Robert C. McLeester of the Botany Department of the University of Minnesota for the excellent specimens of peyote cacti.

(17) E. Späth and J. Bruck, *Ber.*, **71**, 1275 (1938).

Rimocidin. II. Oxygenation Pattern of the Aglycone[1]

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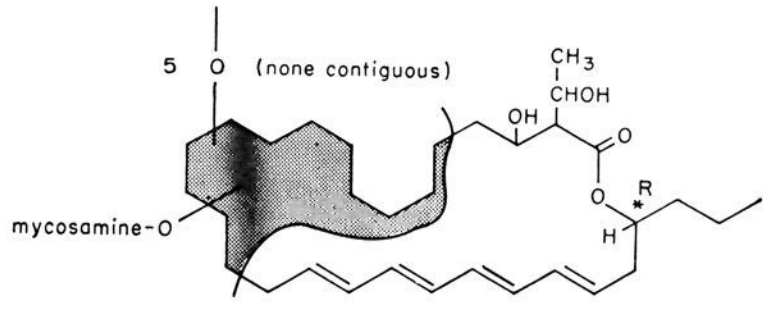
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received March 26, 1966*

Abstract: Isolation of 2-heneicosyl-6-(3-methylpentyl)tetrahydropyran and 2-(9-methylundecyl)-6-pentadecyltetrahydropyran as products of a reductive degradation sequence from rimocidin has proved the presence of oxygen functions at C-5, C-9, C-11, and C-15 in the antibiotic. That the oxygen function at C-11 is a keto group has been shown by the isolation of 2-ethyl-11-oxotriacontanoic acid as the major product of high pressure hydrogenation of rimocidin at 290–296°. These facts in addition to the data published previously constitute a complete proof of the structure of rimocidin aglycone.

Evidence reported in the preceding paper[2] established partial structure **1** for rimocidin. We shall describe here the results of experiments which establish the location and nature of each of the six remaining oxygen functions in the aglycone. The utility of the phosphorus–hydriodic acid method for the determination of the carbon skeleton of a macrolide by conversion to the "parent" hydrocarbon has been amply demonstrated.[2–4] In the earliest paper[3] we also described the isolation of 7,21-dimethyltritriacontane from fungichromin by a different method which did not involve acidic conditions at any stage. Although the over-all yield of hydrocarbon was very low, the method was of interest to us in attempting to locate the position of the glycosidic linkage in rimocidin.



1

Perhydrorimocidin[2] on treatment with lithium aluminum hydride for 2 days at room temperature gave a polyol from which a polytosylate was prepared. From the mixture of products obtained by drastic lithium

(1) Support was provided in part by the National Institutes of Health through Public Health Research Grant AI-02241-08. Acknowledgment is made to Chas. Pfizer and Co. for a generous gift of rimocidin sulfate.

(2) A. C. Cope, E. P. Burrows, M. E. Derieg, S. Moon, and W. Wirth, *J. Am. Chem. Soc.*, **87**, 5452 (1965).

(3) A. C. Cope, R. K. Bly, E. P. Burrows, O. J. Ceder, E. Ciganek, B. T. Gillis, R. F. Porter, and H. E. Johnson, *ibid.*, **84**, 2170 (1962).

(4) O. Ceder, *Acta Chem. Scand.*, **18**, 77 (1964).

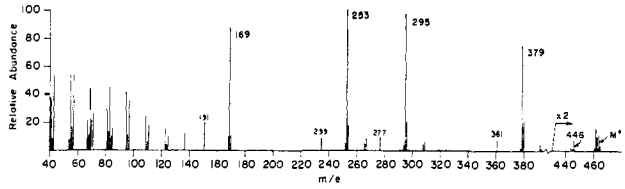
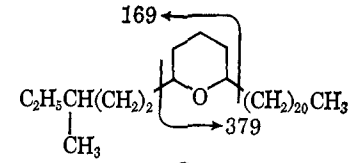


Figure 1. Mass spectrum of tetrahydropyrans from rimocidin.

aluminum hydride reduction of the polytosylate followed by acid hydrolysis (assuming an intact glycoside up to the last step) we hoped to isolate a C_{32} alcohol. The position of the hydroxyl group in this compound would mark the position of the glycoside in the original antibiotic. The C_{32} alcohol eluded us, but an investigation of the products of this sequence of reactions did provide some needed information. Not surprisingly, oxygen–sulfur bond cleavage competed favorably with carbon–oxygen bond cleavage during lithium aluminum hydride reduction and mixtures of polyhydroxy compounds were the predominating products. Our investigations were confined to the less polar products which could be separated from the polyols by chromatography on alumina. A major component, isolated by a combination of alumina chromatography and gas chromatography, had a composition most closely approximating $C_{32}H_{64}O_2$ and its mass spectrum indicated a molecular weight of 480. Its infrared spectrum proved the presence of at least one hydroxyl group. There were strong infrared bands in the C–O stretching region but no evidence for unsaturation, and the material was unchanged on catalytic hydrogenation. Thus the second oxygen atom was present as a cyclic ether. Since no single structure could be deduced to account for the major peaks in the mass spectrum,[5] the material was apparently a mixture of isomers which defied separation attempts.

The mixture was oxidized by chromium trioxide in acetic acid to a mixture of keto ethers ($\nu_{max}^{CCl_4}$ 1710 cm^{-1}) whose structures again could not be deduced from the mass spectrum of the mixture.[6] Wolff–Kishner reduction gave a major product which after separation from unchanged keto ether by gas chromatography had a mass spectrum displaying a weak molecular ion peak at *m/e* 464 and major peaks at *m/e* 169, 253, 295, 379, and 421. It was difficult to rationalize this last peak in terms of a cyclic ether structure, and the suspicion that it was due to the presence of 3-methyluntriacontane[2] (not separable from the cyclic ethers by gas chromatography) was confirmed by chromatography of the mixture on silicic acid. The hydrocarbon was removed by elution with hexane and the cyclic ethers were eluted with 1:20 benzene–hexane. The structures of the cyclic ethers, 2-heneicosyl-6-(3-methylpentyl)tetrahydropyran (**2**) and 2-(9-methylundecyl)-6-pentadecyltetrahydropyran (**3**), followed unambiguously from the mass spectrum of the mixture (Figure 1).[7] The alternative pair of isomeric tetrahydropyrans **4** and **5** was ruled out due to the previously established location of the tetraene system in rimocidin (C-18 through C-25).[2]



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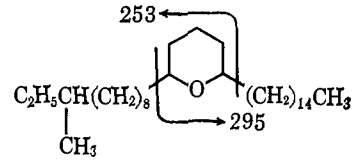

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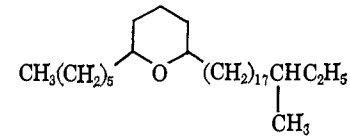
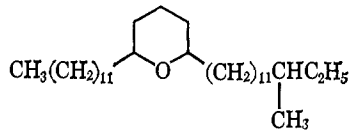


4



5

At present we have no explanation for the substantial M − 1 and M − 2 peaks present in the mass spectrum of the tetrahydropyran mixture. Similarly M − 2 and M − 4 peaks of somewhat greater intensity than the molecular ion were found in the spectrum of the hydroxytetrahydropyran precursor,[5] and in the spectrum of the ketotetrahydropyrans[6] a M − 2 peak of nearly one-half the intensity of the molecular ion was found. No other spectral evidence indicated olefinic impurities in the samples, and the mass spectra were unchanged after catalytic hydrogenation. The mass spectrometer was equipped with an all-glass inlet system[8] and furthermore a tetrahydropyran which was subsequently synthesized showed no spurious peaks in the molecular ion region.

The formation of a cyclic ether on treatment of a suitable tosylate with lithium aluminum hydride is not without precedent, at least for a five-membered ring. 7-Oxabicyclo[3.2.1]octane was the only product reported from lithium aluminum hydride reduction of 3-hydroxycyclohexanemethyl tosylate.[9] Presumably an internal displacement mechanism similar to that proposed by Goering and Serres was operative in our more complex case.

To confirm the identification of the two tetrahydropyrans as well as to substantiate the formation of six-membered cyclic ethers on treatment of tosylates of 1,5-diols with lithium aluminum hydride, an unsymmetrical 2,6-dialkyltetrahydropyran was synthesized utilizing this reaction (see Scheme I). Solutions of the Grignard reagents prepared from 1-bromodecane and

(5) Above *m/e* 130 the major peaks, in order of decreasing relative abundance, were at *m/e* 169, 253, 297, 151, 211, 295, 311, 462 (M − 18), 478, 267, 377, 393, 476, 392, and 480 (M^+).

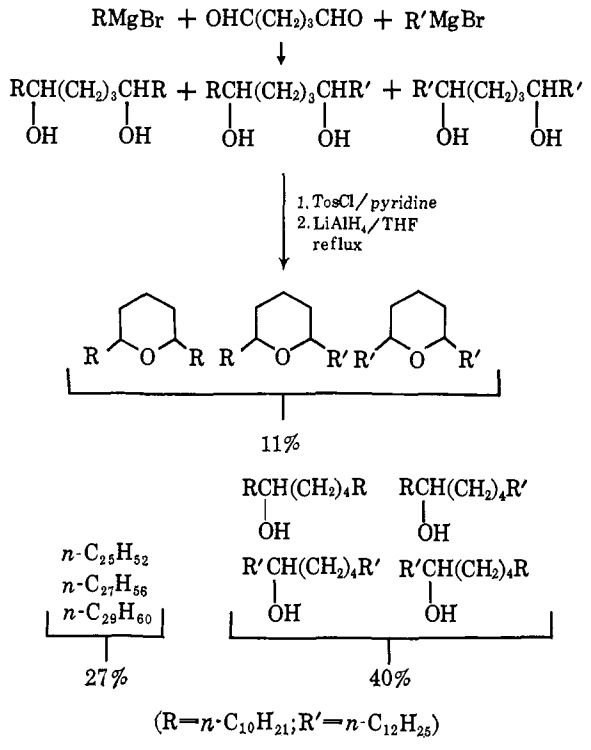
(6) The major peaks above *m/e* 130 were, in order of decreasing relative abundance, at *m/e* 169, 211, 393, 151, 478 (M^+), 295, 253, 281, 421, 226, 408, 227, and 476.

(7) The same mixture of tetrahydropyrans **2** and **3** was isolated in low yield when the polyol fractions from alumina chromatography of the products of lithium aluminum hydride reduction of the polytosylate were subjected to a second tosylation followed by lithium aluminum hydride reduction.

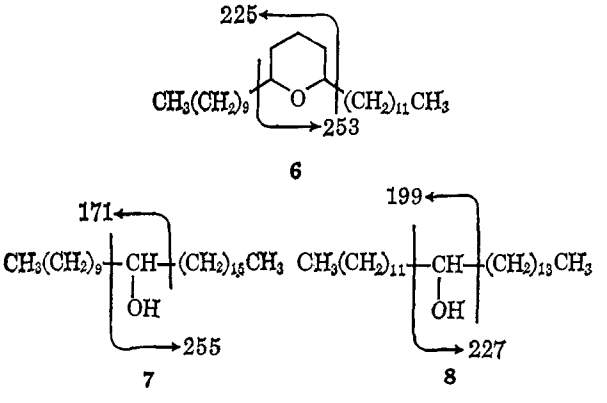
(8) See H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p 32, and references therein cited.

(9) H. L. Goering and C. Serres, Jr., *J. Am. Chem. Soc.*, 74, 5908 (1952).

Scheme I



from 1-bromododecane were added simultaneously to a solution of glutaraldehyde in ether. Treatment of the resulting mixture of three diols with *p*-toluenesulfonyl chloride in pyridine at room temperature gave in 30% yield a mixture of tosylates; 60% of the mixture of diols was recovered unchanged. The mixture of products isolated in high yield after treatment of the tosylates with lithium aluminum hydride in refluxing tetrahydrofuran was partially separated by chromatography on silicic acid. In order of increasing polarity fractions were eluted containing hydrocarbons (27%), tetrahydropyrans (11%), and alcohols (40%).[10] Gas chromatographic analysis of the three groups so separated revealed three components in each. The mass spectrum of the second component of the tetrahydropyran mixture (Figure 2) was in accord with expectation for the desired 2-decyl-6-dodecyltetrahydropyran (**6**). Prominent metastable peaks at *m/e* 190.5 and 218.5, arising from loss of water from the ions of *m/e* 225 and 253 to give the ions of *m/e* 207 and 235, respectively, were found.[11] Similarly the mass spectrum of tetrahydropyrans **2** and **3** from rimocidin displayed the expected metastable peaks at *m/e* 135, 218.5, 260, and 343.5 due to loss of water from the ions of *m/e* 169, 253, 295, and 379, respectively. Analysis of the second component of the alcohol fraction by mass spectrometry revealed a mixture (*ca.* 50:50) of 11- and 13-heptacosanol (**7** and **8**, see Figure 3). Thus it is shown that lithium aluminum hydride reduction of 1,5-ditosylates results in the formation of tetrahydropyrans as minor products. The significance of the isolation of tetrahydropyrans **2** and **3** from rimocidin is clear: their structures necessitate the presence of oxygen functions at C-5, C-9, C-11, and C-15 in the antibiotic. The two remaining oxygen functions must then be placed at C-7 and C-13 in order to satisfy the requirement that none be vicinal or allylic to the tetraene system.



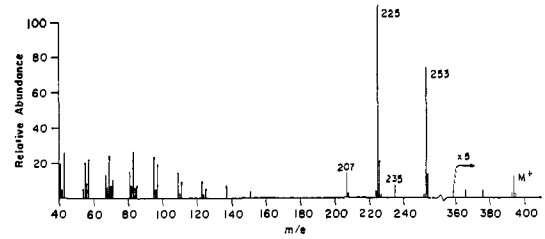


Figure 2. Mass spectrum of 2-decyl-6-dodecyltetrahydropyran.

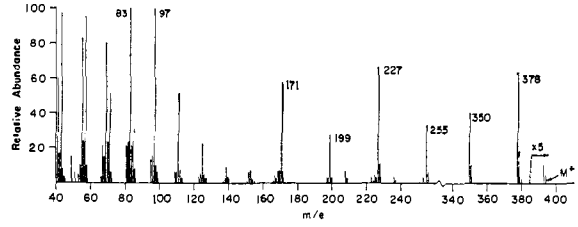


Figure 3. Mass spectrum of 11- and 13-heptacosanol.

Having placed all the oxygen functions it was tempting to believe that mycosamine was attached to the aglycone either at C-7 or C-13 since these were the only positions not involved in tetrahydropyran formation. Unfortunately we soon found that acid treatment after lithium aluminum hydride reduction of the polytosylate in refluxing tetrahydrofuran was not necessary or even desirable for isolation of the mixture of hydroxytetrahydropyrans. An identical mixture resulted (in much higher yield than before) when the products of lithium aluminum hydride reduction were subjected directly to chromatography on alumina. Thus the sugar had been lost at an earlier stage than expected. The finding that lithium aluminum hydride reduction of the polytosylate in tetrahydrofuran at room temperature gave a mixture of different composition from which no hydroxytetrahydropyrans were isolated after alumina chromatography led us to believe that lithium aluminum hydride reduction at higher temperatures occasioned loss of the sugar. Further investigation of the products of the room-temperature lithium aluminum hydride reduction led to no useful conclusion regarding the position of attachment of mycosamine to the aglycone.

A third method of reductive degradation indispensable to the structure determination of macrolides has

(10) The remainder, not eluted with benzene, is presumed to have been largely diols.

(11) For a discussion of the appearance of metastable peaks see K. Biemann, "Mass Spectrometry", McGraw-Hill Book Co., Inc., New York, N.Y., 1962, pp 153–157.

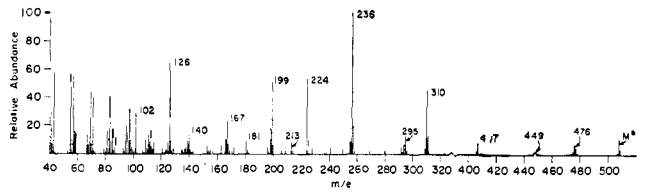
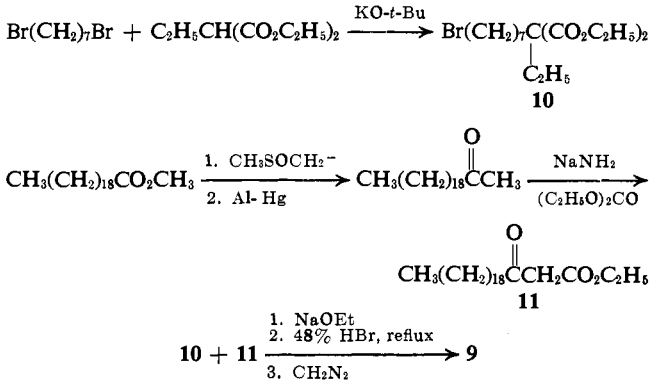


Figure 4. Mass spectrum of methyl 2-ethyl-11-oxotriacontanoate.

been the high-pressure hydrogenation technique originated by Ceder.[12] The presence and location of the keto group and the free carboxyl group in pimaricin were proved by the isolation of 9-oxohexacosanoic acid and 2-tetradecyltridecanedioic acid (among other products) from high-pressure hydrogenation of pimaricin in glacial acetic acid at elevated temperatures (250–300°). Hydrogenation of rimocidin under these conditions gave a mixture of two C_{32} acids (in a combined yield of 45–50%) which was esterified and separated by gas chromatography. The major component had the longer retention time and was identified as methyl 2-ethyl-11-oxotriacontanoate (**9**) by a combination of infrared and mass spectrometry; the minor component was similarly identified as methyl 2-ethyltriacontanoate. The identity of keto ester **9** was confirmed by a synthesis outlined in Scheme II.

Scheme II



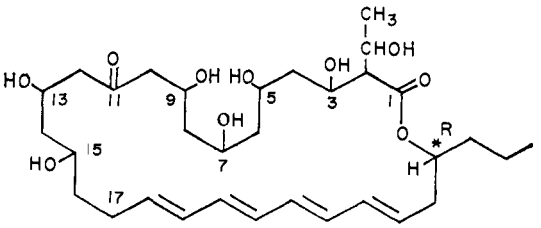
The mass spectra of long-chain keto esters have been amply described,[12,13] and that of keto ester **9** (reproduced in Figure 4) is entirely in accord with the assigned structure and shows no peaks attributable to any other isomer. The fragmentation pathways and the metastable peaks (m^*)[11] found which substantiate them are summarized in Scheme III.

The appearance of the second most intense peak in the spectrum at *m/e* 126 provoked some speculation regarding its orgin. A prominent metastable peak was found at *m/e* 71, implicating an ion of *m/e* 224 as the "parent." This suggested the pathway shown in Scheme IV. The initially formed ketene ion could isomerize to either of two possible α,β-unsaturated aldehyde ions, A or B. Fragmentation of ion A with rearrangement would give the ion of *m/e* 126; ion B similarly would yield an ion of *m/e* 140. The latter ion was also present (moderate intensity) in the spectrum and a metastable peak indicating its origin from a parent of *m/e* 224 was found as well (at *m/e* 87.7). The prominent peaks observed at *m/e* 97 and 83 would then arise from the neutral aldehyde fragments C and D, respectively, by ionization and loss of a hydrogen atom. The ion of *m/e* 97 could lose either a formyl or an ethyl group to give one or both of the possible ions of *m/e* 69.

Long-chain keto esters lacking an α substituent apparently do not undergo the rearrangement–fragmentation process summarized in Scheme IV to an appreciable extent, since the corresponding peak is not found in the spectra available from the previous literature.[12,13] Presumably the presence of an α substituent is necessary for the rearrangement of the ketene ion to an α,β-unsaturated aldehyde to compete favorably with other processes.

It was not found possible to separate and identify any of the more polar products from this high-pressure hydrogenation (see the Experimental Section). High-pressure hydrogenation at lower temperatures (150–250°) gave complex mixtures of acetylated products of undetermined structures.

The isolation of keto ester **9** established the presence of a keto group at C-11 in rimocidin. The survival of the keto group under these drastic hydrogenation conditions also proved that the sixth molar equivalent of hydrogen absorbed in acetic acid at room temperature and atmospheric pressure[2] was due to hydrogenolysis of a second hydroxyl group β to the lactone carbonyl rather than to hydrogenation of a keto group. The structure of rimocidin aglycone can now be formulated as **12**.[14] Further work designed to locate the point of attachment of mycosamine to the aglycone, which will complete determination of the structure of rimocidin, will be the subject of a final paper.



12

Experimental Section[15]

Isolation of a Mixture of Isomeric C_{32} Hydroxytetrahydropyrans from Rimocidin. Perhydrorimocidin[2] (7.50 g) was stirred for 40 hr at room temperature with 8 g of lithium aluminum hydride in 600 ml of tetrahydrofuran (THF). Work-up was accomplished by slow addition of water (18 ml) to the cooled, stirred mixture followed by filtration through magnesium sulfate–Celite. The filtrate was

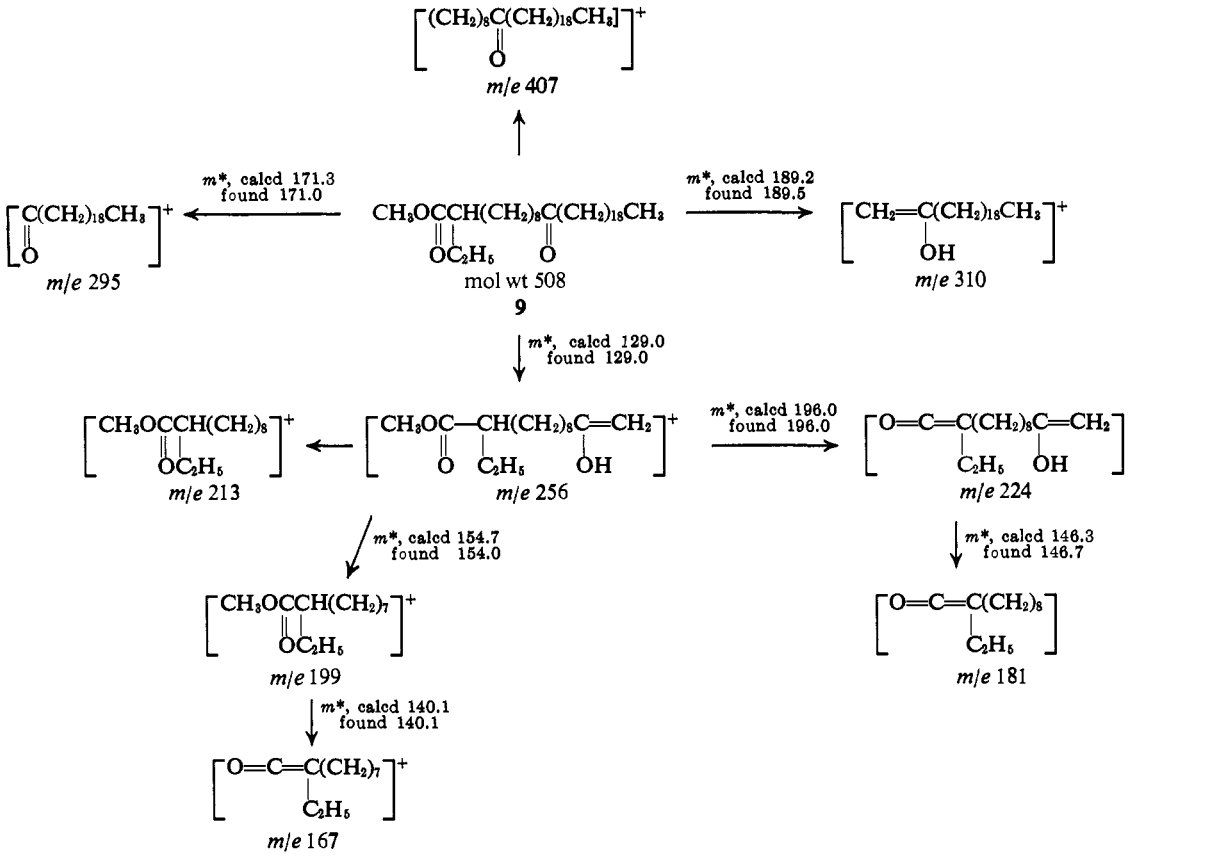
(12) O. Ceder, J. M. Waisvisz, M. G. van der Hoeven, and R. Ryhage, *Acta Chem. Scand.*, **18**, 83 (1964). We are grateful to Dr. Ceder for informing us of his results and for furnishing us a detailed description of the method prior to publication.

(13) R. Ryhage and E. Stenhagen, "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, pp 430, 431, and references cited therein.

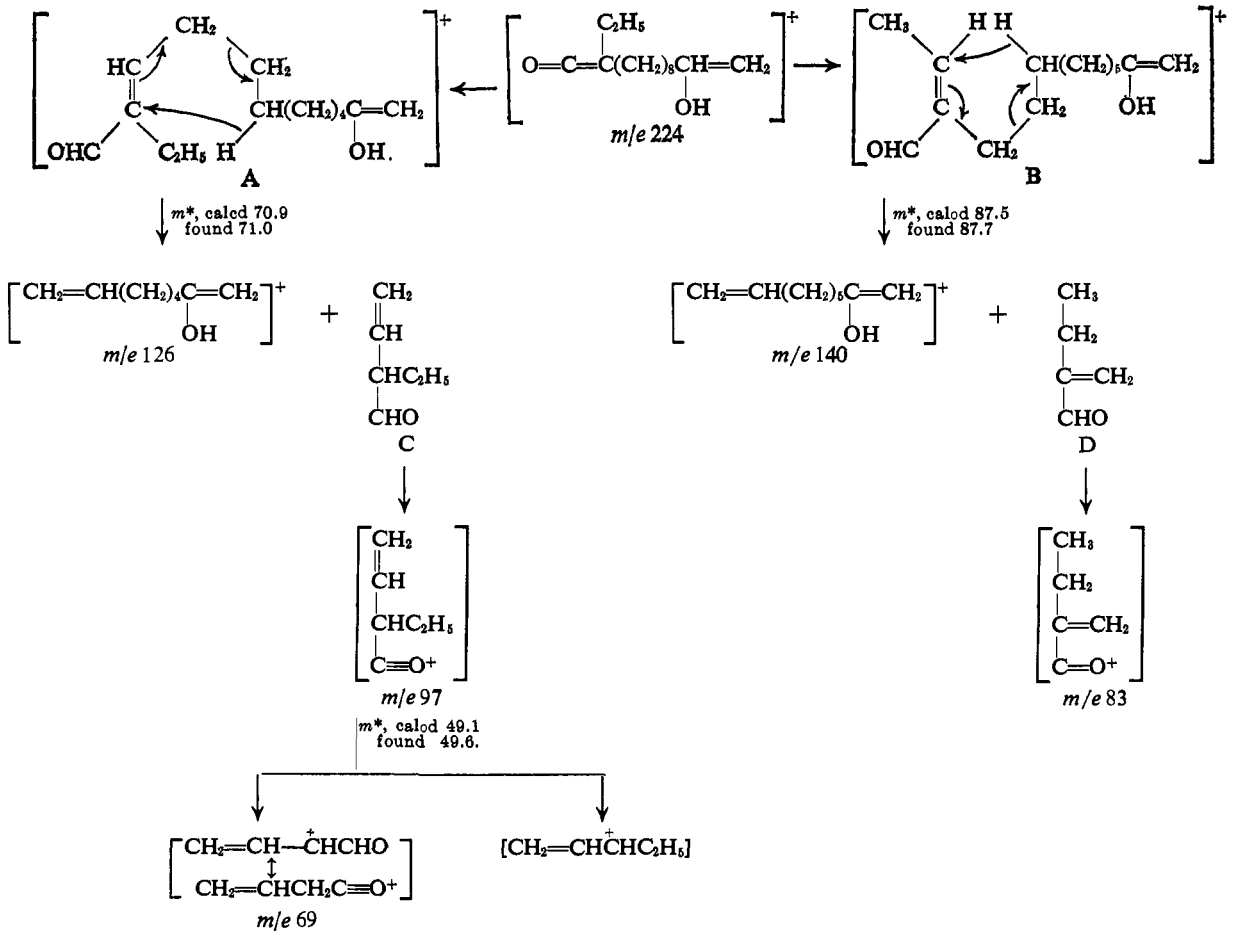
(14) One notes the possibility of hemiketal formation with the hydroxyl group at C-7 or the one at C-15. It is not established at this time which if either possibility is correct.

(15) A Hitachi Perkin-Elmer RMU-6D mass spectrometer was used unless noted otherwise. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian Associates A-60 instrument. Analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, unless noted otherwise. Gas chromatographic (vpc) analyses and collections (temperatures 240–300°) were made using an F and M Model 720 instrument equipped with 2 ft × 0.25 in. columns packed with 3 or 10% silicone rubber (SE-30) on 60–80 mesh Chromosorb W, and an F and M Model 810 (with thermal conductivity detector only) equipped with a 4 ft × 0.25 in. 5% silicone rubber column (on 60–80 mesh diatoport S). Solvents were removed under reduced pressure using a rotary evaporator, and magnesium sulfate was used as a drying agent throughout.

Scheme III



Scheme IV



evaporated to dryness and the filter cake was extracted with THF in a Soxhlet extractor yielding a total of 5.45 g of polyol. To a stirred solution of the polyol in pyridine (30 ml) at 0° was added dropwise a cold solution of 20 g of *p*-toluenesulfonyl chloride in pyridine (125 ml), and the mixture was allowed to stand at 5° for 5 days. Most of the pyridine was removed by evaporation below room temperature and the residue was dissolved in chloroform and washed with cold sodium chloride solution containing 0.5% sulfuric acid until the washings had pH 5–6 (three portions). The crude polytosylate (20 g) obtained after drying the chloroform solution at 5° and removing the solvent had no infrared absorption in the hydroxyl region. It was dissolved in THF (500 ml) and stirred under reflux for 40 hr with lithium aluminum hydride (16 g). A work-up similar to that described for the first lithium aluminum hydride reduction was employed; 30 ml of water was added very slowly with cooling and vigorous stirring. Evaporation of the filtrate yielded 2.35 g of a colorless, odorless, mixture; Soxhlet extraction of the filter cake gave 5.62 g of foul-smelling orange material. The former mixture was partially separated by chromatography on Merck acid-washed alumina (70 g). Fractions eluted with pentane and with 1:50 to 1:10 ether–pentane mixtures (0.21 g) were mixtures of aromatic sulfur-containing materials. Fractions eluted with ether (1.09 g) contained the materials of interest, but it was not possible to separate a major component by repeated chromatography of these fractions. Analysis by vpc revealed a complex mixture of at least seven components, with a major peak (50–60%) having a retention time slightly longer than that of *n*-dotriacontane. Significant spectral data obtained from collected samples of this major component were the following: infrared (carbon tetrachloride solution) 3600 (weak), 3460 (weak), 1090 (strong), and 1030 cm^{-1} (medium); nmr (carbon tetrachloride solution) δ 0.87 (poorly resolved triplet) and 2.8–3.7 (broad multiplet). The mass spectrum is summarized in footnote 5. Hydrogenation of a collected sample (15.5 mg) in ethyl acetate (2 ml) over platinum as catalyst (5 mg of platinum oxide) produced no change in the mass spectrum.

Anal. Calcd for $C_{32}H_{64}O_2$: C, 79.93; H, 13.42. Calcd for $C_{32}H_{64}O_3$: C, 77.35; H, 12.98. Found: C, 78.90; H, 12.95.

Conversion of the C_{32} Hydroxytetrahydropyrans to 2-Heneicosyl-6-(3-methylpentyl)tetrahydropyran and 2-(9-Methylundecyl)-6-pentadecyltetrahydropyran. The collected hydroxytetrahydropyran mixture (14 mg) was stirred at 60° for 30 min with chromium trioxide (12.5 mg) in glacial acetic acid (0.3 ml). The mixture was diluted with 5 ml of water and extracted twice with ether. The ether extracts were shaken successively with 5% sodium hydroxide and sodium chloride solution, dried, and evaporated. Gas chromatographic analysis of the white solid residue (10 mg) revealed a major component (65%) with a retention time approximately the same as that of the starting hydroxytetrahydropyrans and a minor component (35%) with a much shorter retention time. The infrared spectrum of the major component had bands at 1710, 1080, and 1035 cm^{-1} and no absorption in the 3600–3200-cm^{-1} region. Its mass spectrum is summarized in footnote 6.

The remainder of the mixture of oxidation products (9 mg) was heated at 190° for 5 hr with triethylene glycol (0.1 ml), 85% hydrazine hydrate (40 μl), and potassium hydroxide (21 mg). After cooling, the mixture was diluted with water (2 ml) and 6 *N* hydrochloric acid (5 drops) and extracted twice with pentane. Gas chromatographic analysis of the residue (7 mg) after evaporation of the solvent revealed a mixture of two major components in a relative ratio 3:2 in order of increasing retention time, plus a number of minor components of lower molecular weight. The major component of longer retention time was identified on the basis of its infrared spectrum as the previously characterized mixture of ketotetrahydropyrans. The other major component had no infrared absorption in the hydroxyl or carbonyl regions and its mass spectrum showed major peaks at *m/e* 169, 253, 295, 379, and 421. A collected sample was dissolved in hexane and chromatographed on a column of silicic acid (100–150 mg) in hexane. The hexane eluate was discarded and the tetrahydropyrans contained in the fraction eluted with 1:20 benzene–hexane were collected by gas chromatography for analysis by mass spectrometry. The result is depicted in Figure 1.

Synthesis of 2-Decyl-6-dodecyltetrahydropyran (6). A. Grignard Reaction. A solution of glutaraldehyde in dry ether was prepared as follows. 2-Ethoxy-3,4-dihydropyran (9 g, supplied by K and K Laboratories) was added with stirring to a solution of 1.9 ml of concentrated hydrochloric acid and 22.5 ml of water, and stirring was continued for 2 hr. The mixture was neutralized with sodium bicarbonate, saturated with sodium chloride, and extracted with three 30-ml portions of ether. The ether extracts were stirred for 1.5 hr with magnesium sulfate, filtered, and then stirred for 1 hr with Linde molecular sieve 4A. Immediately prior to addition of the Grignard reagents, the molecular sieve was separated by filtration and the filtrate was concentrated to 10 ml.

While the glutaraldehyde solution was being dried two Grignard reagents were prepared. 1-Bromodecane (7.60 g), magnesium (0.826 g), and ether (35 ml), and 1-bromododecane (8.56 g), magnesium (0.826 g), and ether (40 ml) were used. The Grignard reagents were decanted under nitrogen atmosphere into two dropping funnels connected to a three-necked flask containing the solution of glutaraldehyde in ether. The mixture was stirred magnetically while the Grignard reagents were added dropwise simultaneously, and stirring was continued overnight (18 hr). Water was added dropwise with external cooling, followed by 2 *N* hydrochloric acid until the aqueous layer was strongly acidic. The aqueous layer was discarded and the remaining organic layer, consisting of an ether solution with suspended white particles, was shaken with two portions of water. A mixture (1.5 g) consisting only of the desired three diols by vpc analysis was obtained by filtration of the ether suspension. This ether-insoluble material could be recrystallized quantitatively from absolute ethanol. Its infrared spectrum (Nujol mull) showed significant absorption at 3300 (broad), 1350, 1135, and 1115 cm^{-1}. The remainder of the reaction product (11.4 g), obtained by evaporation of the ether solution, was not investigated except to note that it was a complex mixture of low to high molecular weight compounds partially separable by a combination of alumina chromatography and vpc.

B. Tosylation. The mixture of diols (1.47 g) was only partially soluble in 15 ml of pyridine. To the stirred suspension was added a solution of *p*-toluenesulfonyl chloride (1.36 g, roughly 2 molar equiv) in pyridine (10 ml). Stirring was continued for 16 hr after which time water (100 ml) was added with external cooling, followed by sodium chloride and ether. The mixture was shaken thoroughly and the layers were separated. Sixty per cent of the mixture of diols (0.87 g), insoluble in either layer, was recovered unchanged. The ether layer was washed with portions of sodium chloride solution containing *ca.* 5% sulfuric acid until the aqueous layer had pH 3 and then with two portions of sodium chloride solution, and dried. A mixture of tosylates (0.72 g) was obtained. Further extraction of the original aqueous solution with ether followed by washing as above yielded no additional material.

C. Lithium Aluminum Hydride Reduction. A solution of the mixture of tosylates in 20 ml of THF was stirred under reflux for 20 hr with 0.5 g of lithium aluminum hydride. Water (1.5 ml) was added with stirring and cooling, and the mixture was filtered through magnesium sulfate. The filtrate was evaporated to dryness and of the residual semisolid (0.45 g) a portion (127 mg) was chromatographed on 2.3 g of silicic acid. A mixture of hydrocarbons (34 mg, 27%) was eluted with hexane, a mixture of tetrahydropyrans (15 mg, 11%) was eluted with 1:20 benzene–hexane mixtures, and a mixture of alcohols (51 mg, 40%) was eluted with 1:4 to 1:1 benzene–hexane mixtures. Gas chromatographic analysis of the hydrocarbons and the alcohols revealed in each case three peaks in a relative ratio 1:1.5:1 in order of increasing retention times. The tetrahydropyran mixture also showed three peaks but in an approximate relative ratio of 1:2:3, with retention times identical with those of *n*-pentacosane, *n*-heptacosane, and *n*-nonacosane, respectively. The mass spectrum of the second component, depicted in Figure 2, proved its homogeneity and its identity as 2-decyl-6-dodecyltetrahydropyran (**6**). Repetition of the silicic acid chromatography followed by vpc provided an analytical sample.

Anal. Calcd for $C_{27}H_{54}O$: C, 82.16; H, 13.79. Found: C, 81.95; H, 14.16.

The composition of the second component of the mixture of alcohols was determined by analysis of its infrared ($\nu_{max}^{CCl_4}$ 3610 cm^{-1}) and mass spectra (Figure 3).

High-Pressure Hydrogenation of Rimocidin. Isolation of Methyl 2-Ethyl-11-oxotriacontanoate and Methyl 2-Ethyltriacontanoate. Rimocidin free base (600 mg), prepared by dropwise addition of 1 equiv of 1 *N* aqueous sodium hydroxide to a stirred suspension of rimocidin sulfate in 1:1 methanol–water (25 ml) followed by filtration and drying over silica gel at 0.1 mm, was dissolved in 8 ml of glacial acetic acid. Hydrogenation was carried out at 290–296° and 3050 psi for 5 hr using 5% palladium-on-alumina (330 mg) catalyst. The mixture was cooled and filtered and the filter cake was extracted with boiling 95% ethanol (50 ml). Filtration of the hot suspension and evaporation of the filtrate yielded 55 mg of a white, crystalline acid ($\nu_{max}^{CCl_4}$ 1705 cm^{-1}). Treatment with diazo-

methane gave a methyl ester, mp 54–55° after one recrystallization from pentane, which was shown by vpc to be a mixture of two components in a ratio 15:85 in order of increasing retention times.[16] The major component had infrared absorption (carbon tetrachloride solution) at 1735 and 1710 cm^{-1}, and its mass spectrum (Figure 4) established its identity as methyl 2-ethyl-11-oxotriacontanoate. A collected sample was recrystallized from pentane for analysis, mp 61.5–63.5°.

Anal. Calcd for $C_{33}H_{64}O_3$: C, 77.89; H, 12.68. Found: C, 77.51; H, 12.55.

The minor component had a single infrared band in the carbonyl region ($\nu_{max}^{CCl_4}$ 1735 cm^{-1}). Its identity as methyl 2-ethyltriacontanoate followed from the mass spectrum, which displayed a strong molecular ion peak at *m/e* 494, the "type H"[17] rearrangement peak at *m/e* 102, and no intense peak at *m/e* 74.

Removal of acetic acid from the original filtrate from the hydrogenation and treatment of the residue with diazomethane gave 347 mg of a mixture of products which was partially separated by chromatography on activity III alumina. The fractions eluted with pentane (61 mg) consisted largely of methyl 2-ethyltriacontanoate with small amounts of unidentified materials of lower molecular weight. Elution with 1:50 ether–pentane gave a total of 76 mg, largely methyl 2-ethyl-11-oxotriacontanoate. Complex mixtures of higher molecular weight compounds (68 mg) were eluted with increasing amounts of ether in pentane. A major component, collected by vpc, appeared on the basis of its infrared ($\nu_{max}^{CCl_4}$ 1735 cm^{-1} only) and mass spectra to be an acetoxy ester. Elution with ether gave additional complex mixtures (55 mg) of nitrogen-containing products exhibiting infrared bands at 1740–1730 and at 1660–1645 cm^{-1}. There appeared to be two major components but attempts to separate or characterize either one were unsuccessful.

Synthesis of Methyl 2-Ethyl-11-oxotricosanoate (9). A. Diethyl Ethyl-(7-bromoheptyl)malonate (10). 1,7-Dibromoheptane, bp 95° (1.6 mm), >99.5% pure by vpc, was prepared (91% yield) by treatment of 1,7-heptanediol (Aldrich Chemical Co.) with anhydrous hydrogen bromide at 130° for 2 hr. To a stirred solution of potassium (2.50 g) in *t*-butyl alcohol (75 ml, distilled from sodium) at 80° was added 12.0 g of diethyl ethylmalonate (Eastman White Label). Stirring was continued for 15 min, then the solution was cooled and to it was added 2 equiv of 1,7-dibromoheptane (33.0 g). The mixture was stirred at 80° for 3 hr, then cooled. Water was added and the organic materials were extracted with ether, washed with water, and dried. After removal of the solvents, the residue was fractionally distilled. The combined low-boiling fractions, consisting largely of the dibromide by gas chromatographic analysis, weighed 17.6 g. Bromo ester **10** (8.3 g, >98% pure by vpc) was obtained from the intermediate fractions, bp 133–135° (0.1 mm).

Anal. Calcd for $C_{16}H_{29}O_4Br$: C, 52.60; H, 8.00. Found: C, 52.90; H, 7.89.

B. Methylsulfinylmethyl *n*-Nonadecyl Ketone. Arachidic acid (K and K Laboratories) was esterified with diazomethane and the β-keto sulfoxide was prepared quantitatively according to the procedure of Corey and Chaykovsky.[18] After the reaction mixture was poured into water and acidified with 3 *N* hydrochloric acid the crude solid sulfoxide was collected by filtration and dried, mp 94–98°. It was recrystallized from ethyl acetate, mp 98.5–99.5°.

Anal. Calcd for $C_{22}H_{44}O_2S$: C, 70.92; H, 11.90. Found: C, 71.22; H, 12.02.

C. 2-Heneicosanone. The β-keto sulfoxide (9.54 g) was reduced in three portions with aluminum amalgam in 10% aqueous THF at 60–65°.[18] The resulting crude ketone (7.95 g), contaminated with unchanged sulfoxide, was dissolved in benzene and filtered through activity I alumina (80 g). A total of 5.63 g (71%) of pure 2-heneicosanone, mp 60–62° (lit.[19] mp 61°), was obtained from the benzene eluate.

D. Ethyl 3-oxodocosanoate (11). A solution of 2-heneicosanone (5.63 g) in warm ether (65 ml) was added dropwise to a stirred suspension of sodium amide (1.42 g) in refluxing ether (10 ml), and the mixture was stirred under reflux for 0.5 hr after addition was complete. Diethyl carbonate (4.30 g) was added and the mixture was stirred under reflux for 4 hr, then poured into an ice-chilled solution of acetic acid (3 ml) and water (100 ml). Additional ether (50 ml) was added, the mixture was shaken, and the layers were separated. The ether layer was washed with 2% sodium bicarbonate solution and water, and dried. The crude β-keto ester **11** (6.46 g, 93% yield) obtained after removal of the ether and excess diethyl carbonate had mp 38–48°, $\nu_{max}^{CCl_4}$ 1740, 1715, 1640, and 1620 cm^{-1}. The principal impurity, unchanged 2-heneicosanone, was less soluble in ethanol or pentane and consequently was not removed by recrystallization. Chromatography of a portion (236 mg) of the crude ester on silicic acid (3 g) in carbon tetrachloride yielded pure **11** (24 mg), mp 49.5–51.5°, in the last fractions. The remainder of material eluted (early and middle fractions) consisted of mixtures.

Anal. Calcd for $C_{24}H_{46}O_3$: C, 75.34; H, 12.12. Found: C, 75.33; H, 12.11.[20]

E. Methyl 2-Ethyl-11-oxotriacontanoate. To a stirred solution of sodium (100 mg) in absolute ethanol (5 ml) at 60° was added a slurry of crude β-keto ester **11** (1.66 g) in warm ethanol (50 ml). The ester dissolved immediately. A solution of bromo ester **10** (1.63 g) in ethanol (5 ml) was added and the mixture was stirred under reflux for 4 hr. About one-half of the ethanol was removed by distillation, and to the cooled residue were added water (50 ml) and ether (75 ml). The layers were separated and the organic layer was washed twice with water and dried. The solvents were evaporated to a white solid residue, *ca.* 3 g. A portion (1.68 g) of this crude tricarboxylic ester was stirred at 145° with 48% hydrobromic acid for 4 days. (Similar treatments for shorter periods resulted in incomplete hydrolysis and decarboxylation of both the β-keto ester and the malonic ester groups.) After cooling, the hydrobromic acid was decanted and the residual semisolid ($\nu_{max}^{CCl_4}$ 1705 cm^{-1} only) was taken up in ether, washed twice with water, dried, and esterified with diazomethane. The ether solution was filtered through Merck acid-washed alumina. Analysis by vpc of the crude solid ester so obtained (1.12 g) revealed a major component (at least 95% of the mixture, exclusive of an unidentified component of very short retention time) with the same retention time as keto ester **9** from rimocidin. The mass spectrum of a collected sample was identical with that discussed previously.

(16) The mass spectrum of the mixture established its content even before it was separated by vpc. We thank Mr. David W. Thomas for determining this spectrum, on a CEC 21-103C mass spectrometer.

(17) See ref 11, p 126.

(18) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).

(19) G. T. Morgan and E. Holmes, *J. Soc. Chem. Ind.* (London), **44**, 108-10T (1925).

(20) Performed by Dr. S. M. Nagy of this department.