were evaporated under reduced pressure. Dilution with water, extraction with chloroform, and chromatography over silica gel (hexane–ethyl acetate 3:2 → 1:1) gave 312 mg of **6** as a gum: ir 3460 (br), 1760, 1740, and 1720 cm^{-1}; *m/e* (%, composition) 406 (M, 6, $C_{22}H_{30}O_7$), 307 (1, $C_{17}H_{23}O_5$), 291 (8, $C_{17}H_{23}O_4$), 290 (2, $C_{17}H_{22}O_4$), 249 (4, $C_{15}H_{21}O_3$), 248 (17, $C_{15}H_{20}O_3$), 231 (21, $C_{15}H_{19}O_2$), 230 (50, $C_{15}H_{18}O_2$), 175 (32, $C_{12}H_{15}O$), 157 (100, $C_{12}H_{13}$), 156 (41, $C_{12}H_{12}$), and 99 (56, $C_5H_7O_2$). The gum could not be purified satisfactorily, but the high-resolution mass spectrum was in accord with the postulated empirical formula.

Anal. Calcd for $C_{22}H_{30}O_7$: mol wt 406.1990. Found: mol wt (mass spectrum) 406.1989.

Hydrolysis of 6.—A solution of 300 mg of **6** in 10 ml of aqueous methanol (80%) was stirred with 229 mg of potassium hydroxide at room temperature under nitrogen for 24 hr. The solvents were removed and the residue was diluted with water. Extraction with chloroform and chromatography over silica gel (hexane–ethyl acetate 3:2) gave 39 mg of **7**: mp 167–171°; ir 3460, 3400, and 1755 cm^{-1}; nmr (acetone-d_6) 1.19 (3 H, d, $J \sim 7$), 1.77 (3 H, d, $J \sim 1$), 1.92 (3 H, br) 4.10 (1 H, dd, $J \sim 2$ and 5), 4.22 (1 H, m), 5.11 (1 H, dd, $J \sim 11$ and 1), and 5.40 ppm (1 H, dd, $J \sim 11$ and 1); *m/e* (%) 266 (M, 11), 248 (26), 230 (18), and 95 (100).

Anal. Calcd for $C_{15}H_{22}O_4$: mol wt 266.1518. Found: mol wt (mass spectrum) 266.1501.

Epoxidation of 7.—A solution of 30 mg of **7** in 2 ml of chloroform was allowed to stand with 22 mg of *m*-chloroperbenzoic acid at room temperature for 1 hr. The reaction mixture was evaporated and chromatographed over silica gel (hexane–ethyl acetate 3:2) to give 10 mg of **8**, mp 222–225° dec, undepressed on admixture with a sample of dihydroheliangino1 (**8**) prepared from eriodictyol; the ir, nmr, and mass spectra were identical with those of the authentic sample.

Preparation of Dihydroheliangino1 (8) from Eriodictyol (5b).—A solution of 391 mg of eriodictyol in 10 ml of methanol was stirred with 390 mg of sodium borohydride at 0° for 0.5 hr. The reaction mixture was acidified, evaporated at reduced pressure, diluted with water, and extracted with chloroform. The crystalline residue obtained was dissolved in 20 ml of aqueous methanol (80%) and heated with 200 mg of potassium hydroxide on a steam bath under nitrogen for 4 hr. The reaction mixture was acidified and the solvents were removed under reduced pressure. Dilution with water and continuous extraction with ether for 48 hr afforded 264 mg of dihydroheliangino1 (**8**), which on recrystallization from ethyl acetate had mp 224–225° dec (reported mp 219–220° dec,[7] 202–203°[5]). The nmr spectrum was identical with that of an authentic sample, whereas the ir spectrum of our sample (KBr) differed in a few minor details from the spectrum recorded by Torrance, *et al.*[7] These discrepancies can probably be ascribed to differences in crystal forms of the two samples.

Registry No.—**1**, 40328-96-9; **2**, 40386-87-6; **3**, 40328-97-0; **4**, 40386-88-7; **6**, 40328-98-1; **7**, 40328-99-2.

Acknowledgments.—I. W. wishes to thank the Swedish Tobacco Company for a stipend. We are indebted to Professor T. A. Geissman for a generous sample of eriodictyol and for reference spectra of dihydroheliangino1.

The Total Synthesis of *dl*-Avenaciolide[1]

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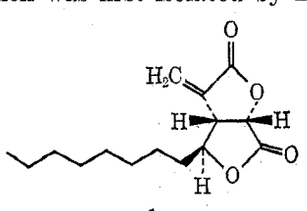
Received March 13, 1973

The total synthesis of the mold product avenaciolide (**1**) is reported using the following sequence. Acylative decarboxylation of tricarballylic acid with nonanoic anhydride afforded the dilactone (**26**) of 3-(1,1-dihydroxynonyl)glutaric acid. Reduction of this dilactone by means of alkaline borohydride then led to *trans*-tetrahydro-2-octyl-5-oxo-3-furanacetic acid (**16**) which was converted *via* its acid chloride to the pyrrolidine amide **32**. Carbomethoxylation of the latter compound afforded the amidolactonic ester **33**. Treatment of this material with sodium hypochlorite solution followed by boiling both the neutral and acidic products with aqueous hydrobromic acid led to the dilactone **35**. Carboxylation of **35** with methyl methoxymagnesium carbonate provided the dilactonic acid **40** which when treated with formaldehyde and diethylamine in buffered acetic acid yielded *dl*-avenaciolide (**1**).

Avenaciolide (**1**) is a naturally occurring antifungal compound which was first isolated by Brookes, Tidd,



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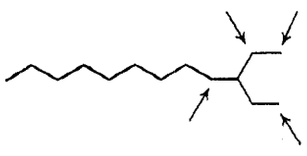
and Turner[2a] from *Aspergillus avenaceus* H. Smith. It was also subsequently obtained from cultures of *Aspergillus fischeri* var. glaber[2b] by investigators at the U. S. Department of Agriculture. The unique bislactonic structure **1**, assigned to avenaciolide by Brookes, *et al.*,[2a] was later confirmed by a more detailed nmr study.[3] More recently 4-isoavenaciolide has been isolated[4] in small quantity during the large-scale preparation of **1**. In addition, the same authors[4] have isolated ethisolide, the 4-isoethyl lower homolog of **1**, from an unidentified species of *Penicillium*.

For the purposes of synthesis, the skeleton of avenaciolide can be looked upon as that of a γ-nonylpentane (**2**), which is oxygenated to varying degrees at the



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points indicated by the arrows but which is lacking the methylene carbon atom of the second lactone ring. With the objective of simplifying the synthesis in its initial stages, we elected to introduce this latter group, last of all. Our initial synthetic attempts were geared therefore to the synthesis of a suitably oxygenated derivative of 3-nonylglutaric acid. An early attempt

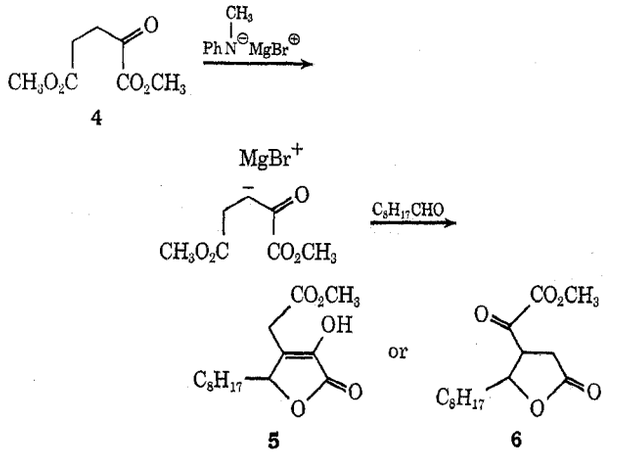
(1) A preliminary account of this work has already been published: W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.*, **91**, 7208 (1969).

(2) (a) D. Brookes, B. K. Tidd, and W. B. Turner, *J. Chem. Soc.*, 5385 (1963); (b) J. J. Ellis, F. H. Stodola, R. F. Vesonder, and C. A. Glass, *Nature (London)*, **203**, 1382 (1964).

(3) D. Brookes, S. Sternhell, B. K. Tidd, and W. B. Turner, *Aust. J. Chem.*, **18**, 373 (1965).

(4) D. C. Aldridge and W. B. Turner, *J. Chem. Soc.*, 2431 (1970).

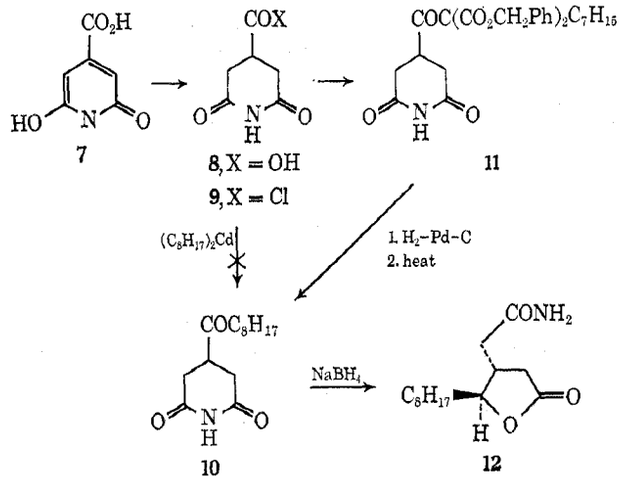
to do this involved the potential Nielsen condensation[5] between the magnesium bromide salt of dimethyl-2-oxoglutarate (**4**) and nonanal. However, neither of the expected lactonic compounds **5** or **6** could be isolated



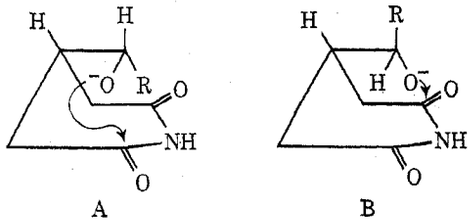
from the reaction. Equally abortive were the attempts to produce **5** or **6** by the diethylamine-catalyzed condensation of nonanal with **4**. In each case the only product that could be isolated was the self-condensation product of nonanal.

Our second attempt at the synthesis of the desired carbon skeleton proved more successful. In this approach the objective was the lactone amide **12** which we thought might be subjected to the Barton lactone synthesis[6] for the construction of the second ring. The synthesis of the desired material was accomplished according to Scheme I.

SCHEME I

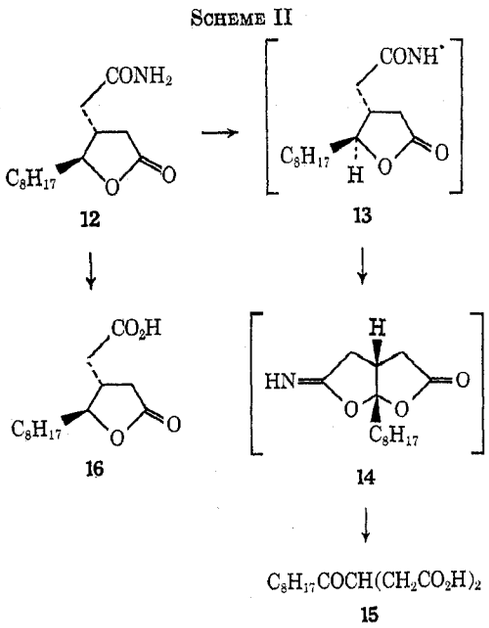


Hydrogenation of citrazinic acid as the sodium salt, using a variation of the literature procedure,[7] easily afforded 3-carboxyglutarimide (**8**) which could be converted almost quantitatively to the acid chloride **9** by means of thionyl chloride containing a trace of dimethylformamide. However, the direct conversion of **9** to the desired ketone **10** using di(*n*-octyl)cadmium could not be achieved, although several variations of the reaction conditions were tried. Nevertheless, the synthesis of **10** from **9** was accomplished in two steps, the first of which involved the acylation of the bromomagnesium salt of dibenzyl *n*-octylmalonate with the acid chloride. This afforded **11** which without further purification was subjected to reductive debenzylation using hydrogen and a palladium catalyst in ethyl acetate solution. Subsequently when this solution was boiled for a brief period, decarboxylation took place cleanly and **10** was produced in good yield. When **10** was treated with sodium borohydride in cold ethanolic solution, reduction and rearrangement occurred smoothly to give the sought-after lactonic amide **12** in good yield. That essentially only one isomer would be obtained in this reaction was anticipated. Attack by the intermediate oxy anion on one of the carbonyl groups of the imide would lead to a transition state (A) in which there is severe eclipsing between the octyl group and the developing acetamide residue. On the other hand, such an attack upon the other carbonyl group (B) leads to a transition state that is strain free.



Having a reasonable supply of **12** in hand it was subjected to the Barton lactonization reaction. Much to our chagrin, however, the carboxamido radical intermediate **13** chose selectively to remove the γ rather than an α proton of the butyrolactone ring. The final product of the reaction after treatment with base was **15**, a compound easily obtained by the hydrolysis of **10**. This reaction undoubtedly proceeds through the intermediate **14** (Scheme II) in keeping with the proposed mechanism.[6] This result, although disappointing, afforded some chemical proof of the stereochemistry assigned to **12**. If **12** had been the cis isomer,

SCHEME II

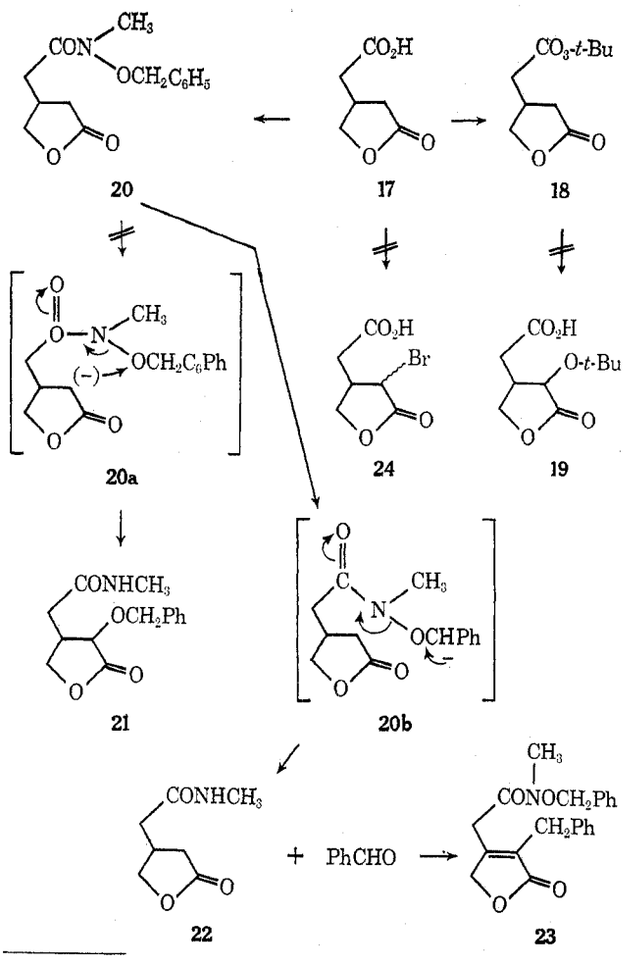


(5) A. T. Nielsen, C. Gibbons, and C. A. Zimmerman, *J. Amer. Chem. Soc.*, **73**, 4696 (1951).
(6) D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 181 (1965).
(7) A. L. Langis and R. Gaudry, U. S. Patent 2,874,158, (Feb 17, 1959).

it seems most unlikely that the γ-hydrogen atom of the butyrolactone ring would have been within reach of the carboxamido radical.

Despite this failure we still felt that the acetamide group of **12** or the corresponding acetic acid residue might be useful for the intramolecular functionalization of the lactone ring at the α position. Although the corresponding acetic acid **16** could be prepared by nitrous acid treatment of **12**, the overall route now appeared cumbersone and tedious, and we looked for an alterative method for its preparation. In the meantime we also examined the functionalization of the α position of the known[8] lactone, **17**, as a model system, since we had a supply of this material at hand from research on a different problem. With the idea of functionalizing the lactonic α position by an internal oxidation, we prepared first of all the per ester **18** and subjected it to the action of potassium *tert*-butoxide. This led only to the regeneration of the starting material **17** and afforded none of the desired product **19**. In a second variation of this procedure the hydroxamic acid derivative **20** was synthesized and subjected to a variety of basic conditions. Only when sodium dimsyl was used was any transformation product obtained. However, the reaction, instead of proceeding *via* **20a** to give the desired lactonic ether **21**, took a different course and the unexpected butenolide **23** (identified by its nmr spectrum) was obtained (Scheme III). The latter undoubtedly arises by the fragmentation

SCHEME III



depicted in **20b** followed by a condensation of starting material **20** and benzaldehyde.

The failure of these reactions is perhaps due more to a lack of certain geometrical requirements than to a lack of feasibility. Eschenmoser, *et al.*,[9] have shown recently that, for tetrahedral carbon at least, an SN2 reaction takes place easily only when the three centers involved have linear geometry. If this then were a necessary requirement for the transformation of **18** to **19** and of **20** to **21**, failure of the reaction could be anticipated. As to feasibility, although to the best of our knowledge no such intramolecular transfer of a functionalized oxygen atom has been reported, an analogous intermolecular example has been published recently by Zinner and Dybowski.[10] They have shown that 1-aminoadamantane when treated with benzoyl peroxide affords the hydroxylamine derivative **25**.

$$\mathrm{AmNH_2} \xrightarrow{(\mathrm{C_6H_5CO_2})_2} \underset{\mathbf{25}}{\mathrm{AmNHOCOC_6H_5}}$$

We also examined the direct functionalization of the α position of the lactone ring of **17**. Halogenation seemed a obvious choice but from the literature it can be gleaned that, although base-catalyzed reactions at this position can be carried out almost as easily as with ketones, acid-catalyzed reactions are extremely difficult to achieve. With respect to halogenation butyrolactones appear to approximate aliphatic esters in reactivity. It is perhaps not surprising then that we were unable to effect bromination of **17** under any of the conditions that we tried and that chlorination at high temperature afforded a complex mixture of products.

Further work, which now led to a successful synthesis of avenaciolide, was conducted with **16** for which a simpler synthesis had by this time been devised. The latter utilized the acylative decarboxylation of tricarballylic acid by acid anhydrides, a reaction which was discovered by Fittig[11] and subsequently was extended by Lawson.[12] It appears to be formally analogous to the later Dakin–West[13] reaction. Initially a discouraging aspect of this approach to **16** was the yields reported by these investigators. These appeared to decrease as the size of the alkyl group of the anhydride increased. Since the Dakin–West reaction and the related acylative decarboxylation of arylacetic acids[14] are both base-catalyzed, we examined the reaction of nonanoic anhydride with tricarballylic acid in the presence of powdered soft glass.[15] Much to our satisfaction the reaction proceeded to give the desired dilactone **26** in 49% yield accompanied by 9% of a highly insoluble self-condensation product of tricarballylic acid. This was identified by its elemental analysis and nmr spectrum as **27**.

The conversion of **26** to **16** was easily accomplished in 91% yield by dissolving it in aqueous potassium

(8) J. K. Mehrotra and A. N. Dey, *J. Indian Chem. Soc.*, **38**, 888 (1961).

(9) L. Tenud, S. Faroog, J. Siebl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970).

(10) G. Zinner and U. Dybowski, *Arch. Pharm. (Weinheim)*, **303**, 488 (1970).

(11) R. Fittig, *Justus Liebigs Ann. Chem.*, **314**, 1 (1901).

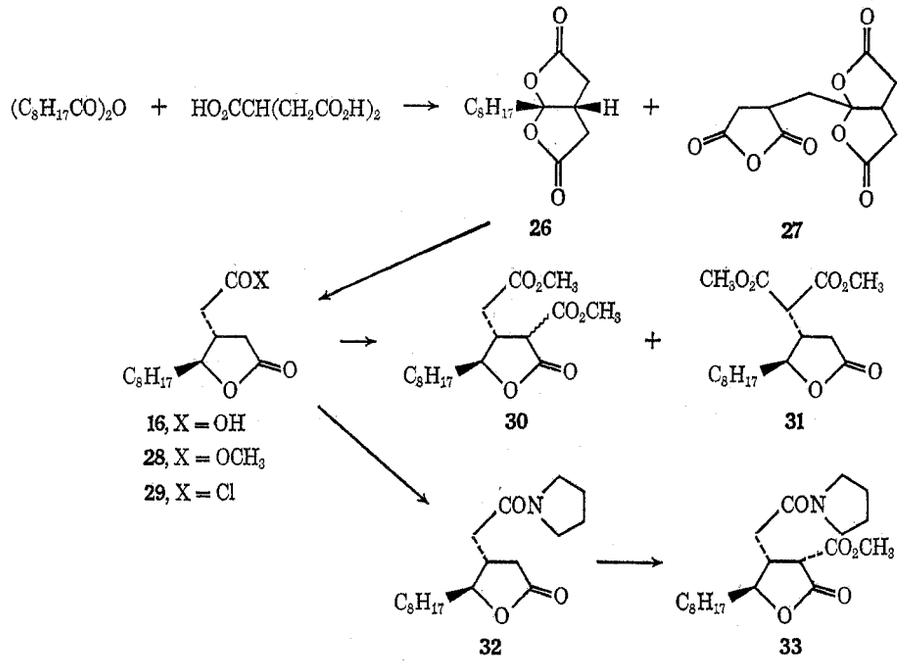
(12) A. Lawson, *J. Chem. Soc.*, 144 (1957).

(13) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91, 745, 757 (1928).

(14) J. A. King and F. H. McMillan, *J. Amer. Chem. Soc.*, **73**, 4911 (1951).

(15) Subsequently we found that this could be omitted provided that the reaction flask had been washed out with a strongly alkaline detergent.

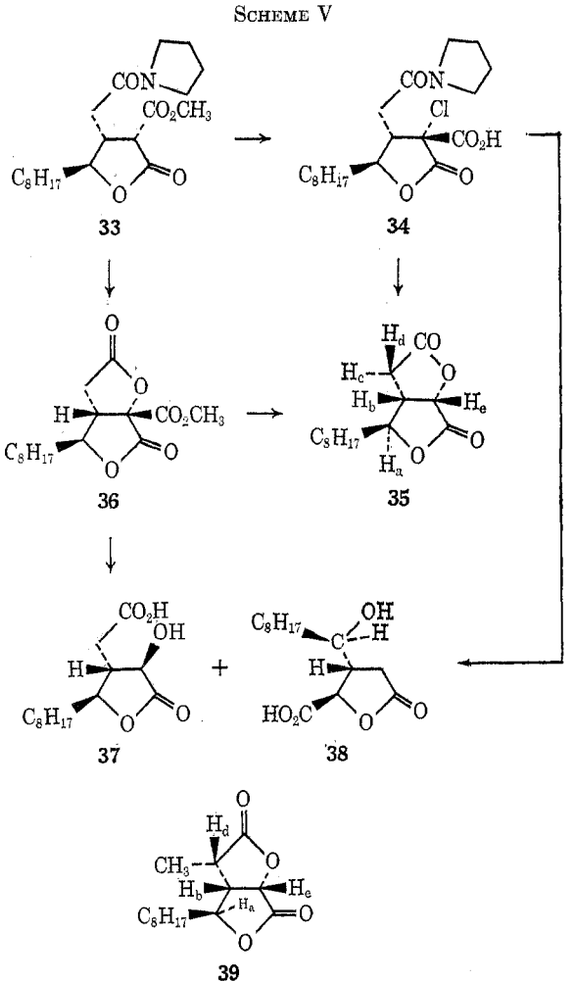
SCHEME IV



hydroxide solution and then adding sodium borohydride. Acidification afforded **16**.

Renewing now our attempts to functionalize the α position of the lactone ring of **16**, we attempted carbomethoxylation of **28** by means of sodium hydride in dimethyl carbonate (Scheme IV). This, however, could not be accomplished cleanly. Although the major product was obviously the desired ester **30**, it was accompanied by approximately 15% of the undesired isomer **31**. To prevent this carbomethoxylation of the acetic residue, we simply converted **16** to the amide[16] **32** *via* the acid chloride **29**. Carbomethoxylation of **32** then led smoothly and exclusively to **33**. We believe that the stereochemistry of **33** is that depicted since protonation of its sodium salt, formed in the reaction of **32** with dimethyl carbonate, should occur on the less hindered face and it could be expected therefore that the substituents at the α,β position of the butyrolactone ring should be cis related. In any event the substance both from its tlc and its nmr spectrum appears to be essentially a single compound. The nmr spectrum shows a very sharp acetate methyl peak at 3.75 ppm and a very minor peak at 3.72 ppm due to the presence of a trace of an isomeric impurity. At a later date the same product was also obtained[17] completely pure when **32** was carboxylated with Stiles' reagent (*vide infra*) and the acid thus produced was methylated with diazomethane. The carbomethoxylated amide **33** reacted rapidly with bromine or iodine in the presence of a weak base such as sodium acetate. However, a particularly convenient method of effecting halogenation of **33** consisted in shaking an ether solution briefly with aqueous sodium hypochlorite. This gave rise to a neutral fraction remaining in the ether layer and an acidic component, isolated from the aqueous phase by acidification. Chromatography of a sample of the neutral material led to a crystalline solid which was characterized by its physical data as the dilactone **36**. (Scheme V). Neighboring-group interactions of this type between amides and halogen and which lead to cyclic imino ethers or butyrolactones have been studied

SCHEME V



(16) Although probably any secondary amine could be used here to deactivate the methylene group of the acetic acid residue, our past experiences with enamines suggested that pyrrolidine would be the most effective.

(17) J. Martin, P. C. Watts, and F. Johnson, *Chem. Commun.*, 27 (1970).

by Stirling.[18] Lactone formation involving a methanesulfonate group and a secondary amide has been noted in the sugar series by Kuzuhara and Fletcher.[19] The acidic fraction from the halogenation of **33** could be crystallized directly and its physical characteristics indicated it to be the acid **34**. The α orientation (below the plane of the ring) assigned to the halogen atom is conjectural but seems likely since no change takes place when **34** is boiled in ethanol. These conditions would be expected[18] to lead to lactone formation if the halogen atom were β oriented.

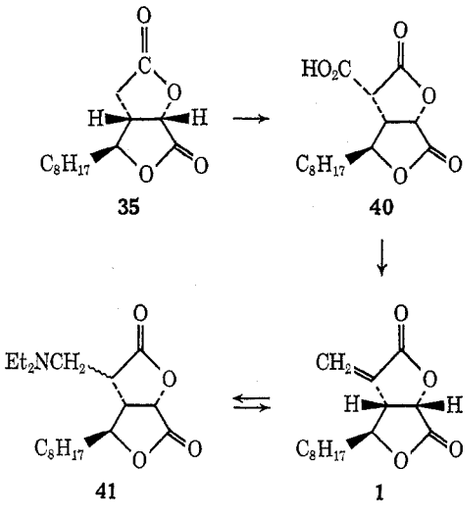
Treatment of either the acidic or the neutral fraction mentioned above with boiling aqueous hydrogen bromide in dioxane followed by azeotropic removal of water from the product gave rise to the desired neutral dilactone **35** and a new acidic fraction. Thus in general practice the total products from the halogenation of **33** were combined and treated as described above to give **35** in 57% yield. The new acidic fraction from this reaction appeared, from its physical characteristics and tlc behavior, to be a mixture of two lactones which probably have structures **37** and **38**. One of these was isolated in small yield by crystallization but no attempt was made to determine its structure.

The stereochemistry of the bislactone is assigned on the basis of a comparison of its nmr spectrum with that of dihydroavenaciolide (**39**). The H_a and H_e protons in both compounds occur at ~4.3–4.5 (multiplet) and at ~5.0 ppm (doublet, J = 7.2 Hz), respectively, and have the same line shapes. The stereochemistry of the methyl group in dihydroavenaciolide (**39**) was shown to be that depicted (*i.e.*, inside the envelope of the two lactone rings) by virtue of the fact that an NOE (~42%) could be observed for H_a when the methyl group was irradiated. This observation not only defines the mode of addition of hydrogen to **39** *but corroborates completely the original assignment*[1,3] *of stereochemistry made to avenaciolide itself.*

The preparation of **35** set the stage for the completion of the synthesis of **1**. We envisioned that, by the introduction of carboxylic function at the $-CH_2-$ group of the upper lactone ring of **35**, we should be able to complete the synthesis by employing the decarboxylative methylenation procedure used by van Tamelen and Bach[20] in the synthesis of protolichesterinic acid. However, initial attempts to carbomethoxylate **35** gave unsatisfactory results and we looked for an alternate method. The use of Stiles' reagent[21] seemed to offer a possible solution, and we were gratified in our expectations to find that the reaction proceeded[17] to give the desired acid, **40**, in excellent yield (Scheme VI). The stereochemistry of the carboxyl group in **40** is assigned the α position since protonation of the intermediate enolate could be expected to occur from the less hindered side, *i.e.*, the β face of the molecule.

Application of the conditions of van Tamelen and Bach[20] to **40** did not lead to avenaciolide. Modification of the procedure by simply treating **40** with diethylamine and aqueous formaldehyde gave mainly an oily material whose nmr and infrared spectra indicated it to be **41**, the diethylamine addition product of avenaciolide. Besides this material, traces of avenaciolide could be isolated but this preparation could hardly be called satisfactory. Consideration of the mechanism by which **41** arises from **40** (it is in fact a variation of the Cope condensation) suggested that the presence of a mild acid was essential, if avenaciolide was to become the major product. Repetition of the reaction in the presence of acetic acid led to complete evolution of carbon dioxide in 1 min. Further brief heating of the reaction mixture then afforded *dl*-avenaciolide in 66% yield identical in all respects, except that of optical activity, with the natural product.

SCHEME VI



Experimental Section

All melting points are corrected. Nmr spectra were recorded in deuteriochloroform on a Varian A-56-60, T60, or HA-100 spectrometer and are not calibrated with the exception noted. Infrared spectra were recorded as films or as Nujol mulls on a Perkin-Elmer 337 spectrometer.

3-Carboxyglutarimide (**8**).—Crude citrazinic acid (10.0 g), as supplied by Chas. Pfizer and Co., was dissolved in a solution of sodium bicarbonate (5.68 g) in water (150 ml). The solution was then hydrogenated at 26° over a 5% rhodium-on-alumina catalyst (0.416 g) under a hydrogen pressure that varied from 3.1 to 0.2 kg cm^{-2}, during the course of the reduction. After 18 hr absorption, which corresponded to 1 mol of hydrogen, ceased. The catalyst was removed by filtration through diatomaceous earth and the filtrate neutralized by the addition of sodium hydrogen sulfate (9.34 g). The solution was then evaporated to dryness under reduced pressure and the residue was extracted with boiling ethanol. Clarification of the solution with charcoal followed by concentration to 70 ml afforded 8.59 g of a tan-colored solid which when recrystallized from the same solvent gave essentially pure 3-carboxyglutarimide (6.54 g), mp 211–212.5° (lit.[7] mp 211–212.5°). A somewhat purer product, mp 214.5–216°, could be obtained by additional crystallization from dioxane, but this was unnecessary for further work.

3-Chlorocarbonylglutarimide (**9**).—Very finely powdered 3-carboxyglutarimide (6.05 g) was added to thionyl chloride (100 g) containing 2–3 drops of dimethylformamide. The mixture was refluxed for 15 min during which time the solution became homogeneous. Removal of the thionyl chloride under reduced pressure afforded a pale yellow solid (6.8 g), mp 113.5° (lit.[22] 118–119°), which was used directly in the subsequent step. This acid chloride is extremely sensitive to moisture and attempts to recrystalize it under normal conditions caused partial conversion to the highly insoluble anhydride.

Dibenzyl Heptylmalonate.—Diethyl heptylmalonate (25.8 g) and benzyl alcohol (37 ml) were heated together in an oil bath at

(18) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960).
(19) H. Kuzuhara and H. G. Fletcher, *J. Org. Chem.*, **33**, 1816 (1968).
(20) E. E. van Tamelen and S. R. Bach, *J. Amer. Chem. Soc.*, **77**, 4683 (1955).
(21) H. L. Finkbeiner and M. Stiles, *J. Amer. Chem. Soc.*, **85**, 616 (1963).
(22) R. F. Struck, H. J. Schaeffer, C. A. Krauth, R. T. Kemp, F. Shealy, and J. A. Montgomery, *J. Med. Chem.*, **7**, 646 (1964).

240–245° until ethanol no longer distilled over. The excess benzyl alcohol was then removed at reduced pressure and the residual liquid was distilled through a short-path condenser to give the desired product (32.2 g), bp 193–201° (0.02 mm), yield 84%.

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.19. Found: C, 75.28; H, 7.89.

3-(1-Oxononyl)glutarimide (10).—Dibenzyl heptylmalonate (14.70 g) was dissolved in dry tetrahydrofuran and the solution cooled to 0°. A solution (37.7 ml) of phenylmagnesium bromide (1.02 *M*) in ether–tetrahydrofuran (1:2) was added dropwise during 15 min. The solution which had reached 30° during this addition was again cooled to 0° and a solution of 3-chlorocarbonylglutarimide (6.8 g) in tetrahydrofuran (45 ml) was added over 30 min. Two hours after initiation of the reaction the solvents were removed *in vacuo*, and the residue was treated with water and benzene. The benzene layer was removed, washed with sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, and taken to dryness under reduced pressure. The resulting viscous oil (22.48 g) was dissolved in methylene chloride and the solution was passed down a column of silica gel (500 g). Elution of the column with methylene chloride (2 l.) afforded crude dibenzyl hepylmalonate (5.15 g) and subsequent elution with methylene chloride containing 20% ethyl acetate led to the desired C-acylated malonate **11** (14.16 g, yield ~100% based on unrecovered dibenzyl heptylmalonate). This material was dissolved in ethyl acetate (200 ml) and hydrogenated over a 10% palladium-on-charcoal catalyst (1.0 g) for 2 hr. The solution was filtered, a trace of copper powder was added, and the mixture was boiled until carbon dioxide evolution was complete (~0.5 hr). After the solution had been washed with saturated sodium hydrogen carbonate solution and then dried over anhydrous magnesium sulfate, the solvent was removed to give crude 3-(1-oxononyl)glutarimide (6.20 g) as a nearly white solid (86.6%). One recrystallization of this material yielded essentially pure material (5.0 g), mp 113.5°. A sample recrystallized for analysis had mp 115–116°. Its infrared spectrum showed imide NH absorption at 3100 and 3190 cm^{-1}, a ketonic bond at 1725 cm^{-1}, and an imide carbonyl doublet 1708 and 1685 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.4; H, 9.1; N, 5.6.

***trans*-Tetrahydro-2-octyl-5-oxo-3-furanacetamide (12).**—3-(1-Oxononyl)glutarimide (2.94 g) and sodium borohydride (0.31 g) were dissolved in ethanol (100 ml), and the resulting solution was stirred at room temperature for 1.5 hr. The solvent was removed under reduced pressure at ~40° and the residue cautiously treated with hydrochloric acid (0.1 *N*, 100 ml). Isolation of the product by methylene chloride extraction yielded a white solid (2.94 g), mp 77–82°. One recrystallization gave 2.1 g of material, mp 84.5–87.5°, suitable for further work and a second gave analytical material, mp 87.5–88°. Its infrared spectrum showed amide NH_2 and carbonyl absorption at 3550, 3215, and 1685 cm^{-1}, respectively, and a γ-lactone band at 1773 cm^{-1}.

Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.81; H, 9.95; N, 5.70.

3-Carboxymethyl-4-oxolauric Acid (15).—The ketoimide **10** (12.2 mg) was heated with 5 *N* hydrochloric acid (10 ml) for 18 hr at ~90°. On cooling the crystalline precipitate which appeared was removed by filtration and dried. The solid (10.7 mg, mp 106.5–108°) after one crystallization from a mixture of ethyl acetate and cyclohexane gave analytically pure material, mp 109–109.5°. Its infrared spectrum had bands at 1715 (ketone) and 1700 cm^{-1} (carboxylic acid).

Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 62.00; H, 8.70.

Attempted Lactonization of *trans*-Tetrahydro-2-octyl-5-oxo-3-furanacetamide.—Lead tetraacetate (1.335 g), iodine (0.778 g), and the lactone **12** (0.257 g) were added to benzene (6 ml), and the mixture was irradiated in a Pyrex vessel with a high-pressure mercury lamp for 5 hr while the mixture was stirred and cooled to 11°. The reaction mixture was diluted with benzene and filtered, and the solid collected was washed with chloroform. The combined filtrates were washed with water followed by saturated sodium hydrogen carbonate solution and were then dried over magnesium sulfate. Removal of the solvents left a partially crystalline residue (0.37 g) which was added to ethanol (20 ml) and water (5 ml) containing potassium hydroxide (1.25 g). The mixture was refluxed for 2 hr and the product after acidification was extracted with ether. The ether solution was in turn extracted with sodium hydrogen carbonate solution; The latter was acidified and the precipitate was collected by filtration and dried *in vacuo*. The faintly tan lustrous plates (0.186 g), mp 106–108°, had an infrared spectrum that was identical with that of the previously prepared 3-carboxymethyl-4-oxolauric acid and a mixture of the two showed no depression in melting point.

3-(1,1-Dihydroxynonyl)glutaric Acid Di-γ-lactone (26).—Nonanoic anhydride (467 g) was stirred and heated at 185° under nitrogen while tricarballylic acid (95.8 g) was added in three portions at 1-hr intervals. The theoretical amount of carbon dioxide (collected in a potassium hydroxide tower) was obtained 7 hr after the start of the reaction.

The reaction mixture was cooled to room temperature, 1 l. of hexane was added, and the resulting slurry was cooled to 0°. The solid material was removed by filtration and washed with hexane (250 ml), then dissolved in hot carbon tetrachloride (300 ml). The residual insoluble substance (5.99 g) had mp 191–194° and is the Fittig self-condensation product (**27**) of tricarballylic acid itself. Recrystallization from acetone afforded the pure material, mp 197.5–198°, whose infrared spectrum showed carbonyl bands at 1780, 1810, and 1845 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}O_7$: C, 51.98: H, 3.97. Found: C, 51.77; H, 3.96.

The carbon tetrachloride solution was taken to dryness under reduced pressure and the resulting solid (100 g) was recrystallized from ether–ethyl acetate. This led to the desired material (67.8 g, yield 49%), mp 84.5–85.5°, which was sufficiently pure for further work. A sample recrystallized for analysis from the same solvent pair had mp 86–87°. Its infrared spectrum showed γ-lactone absorption at 1786 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.06; H, 8.69.

***trans*-Tetrahydro-2-octyl-5-oxo-3-furanacetic Acid (16) and Its Methyl Ester (28).**—(a) The dilactone **26** (65.0 g) was dissolved in hot 1.0 *N* potassium hydroxide solution (774 ml) and sodium borohydride (24.2 g) was added in small portions over 30 min with swirling. The mixture was then heated on a steam bath for 5 hr, cooled to room temperature, and acidified to pH 1 with concentrated hydrochloric acid (~145 ml). The solution was extracted with ether and the ether extract was washed with water, dried over magnesium sulfate, and concentrated to small bulk. Trituration of the oily residue with hexane yielded a crystalline solid (59.9 g, 91.4% yield), mp 55–56°, whose infrared spectrum displayed carbonyl absorption at 1695 and 1762 cm^{-1}. Further recrystallization did not improve the melting point.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.47; H, 9.38.

(b) *trans*-Tetrahydro-2-octyl-5-oxo-3-furanacetamide (**12**, 45.3 mg) was refluxed in 5 *N* hydrochloric acid (20 ml) for 15.5 hr. The product (41.3 mg) was isolated by methylene chloride extraction. It solidified on standing, mp 45–51.5°, and on recrystallization from ether–hexane afforded the pure compound, mp 55–56°, whose infrared spectrum was identical with that of a specimen prepared according to method a above. Treatment of this acid with ethereal diazomethane afforded a quantitative yield of the methyl ester, mp 20–21.5°, whose infrared spectrum showed significant bands at 1737 and 1776 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.77; H, 9.65.

***trans*-β-(1-Hydroxynonyl)-δ-oxo-1-pyrrolidinevaleric Acid γ-Lactone (32).**—The lactonic acid **16** (4.50 g) was dissolved in thionyl chloride (8.5 ml) containing 2 drops of dimethylformamide. After 2 hr at room temperature the solution was heated briefly (3–4 min) on the steam bath and the excess thionyl chloride was removed *in vacuo*. The residue was dissolved in benzene (40 ml) and pyrrolidine (3.1 ml) was then added dropwise to this solution. After 30 min at room temperature the mixture was diluted with ether, washed with dilute hydrochloric acid then water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent left an oil which crystallized from hexane–benzene to give the desired material (4.36 g, 81%), mp 49–51°. A sample recrystallized several times from hexane afforded the pure compound, mp 51–52°, whose infrared spectrum showed bands at 1640 and 1775 cm^{-1}.

Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.86; H, 10.10; N, 4.53. Found: C, 69.91; H, 10.15; N, 4.49.

Methyl [2-Hydroxy-1-(1-pyrrolidinylcarbonyl)methyl]decylmalonic Acid γ-Lactone (33).—(a) A 56% dispersion of sodium hydride in mineral oil (22.0 g) was washed free of the oil with petroleum ether (bp 30–60°) by decantation under dry nitrogen.

The residual hydrocarbon was removed by evaporation and dry dimethyl carbonate (450 ml) containing methanol (100 μl) was added. This mixture was stirred at ~80° while a solution of the lactonic amide **32** (32.0 g) in dimethyl carbonate was added dropwise during 30 min. The mixture was refluxed for 6 hr but after the first 20 min hydrogen evolution became so vigorous that the heating was reduced. The mixture was cooled to room temperature and glacial acetic acid (53 ml) was added to it slowly with stirring. The solution was diluted with water (350 ml) and the product extracted with ether. The ethereal solution was washed with sodium bicarbonate solution and water and then dried over anhydrous magnesium sulfate. Removal of the ether afforded oil (37.8 g) which was chromatographed on silica gel (600 g). Elution with ether and then ethyl acetate yielded **33** as a colorless oil (31.42 g, 82.6%), $n^{24.5}$D 1.4857, whose infrared spectrum (film) showed significant bands at 1777, 1739, and 1640 cm^{-1}. The nmr spectrum (CCl_4) showed a singlet at 3.73 ppm (OCH_3).

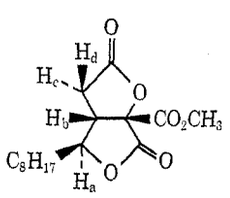
Anal. Calcd for $C_{20}H_{33}NO_5$: C, 65.37; H, 9.05; N, 3.81. Found: C, 65.52; H, 9.15; N, 4.15.

(b) The lactonic amide **32** (1.0 g) was added to 5 ml of a solution (5 ml) of methyl methoxymagnesium carbonate[21] in dimethylformamide under nitrogen, and the solution was then heated for 6 hr at 130° while a slow stream of N_2 gas was bubbled through the liquid. The mixture was then poured into ice cold 6 *N* hydrochloric acid and ether and shaken thoroughly to dissolve the solid material. The ether extract was washed four times with water and dried ($MgSO_4$) and the ether removed under reduced pressure. The residual solid (0.9 g) had mp 92–98° and after two recrystallizations afforded the pure acid, mp 94.5–95.5°. The nmr spectrum of the compound shows a single fairly sharp peak in the low field region at 10.08 ppm (CO_2H) indicating the presence of only one carboxylic acid.

Anal. Calcd for $C_{19}H_{31}NO_5$: C, 64.56; H, 8.84; N, 3.96. Found: C, 64.12; H, 8.90; N, 4.25.

A specimen of the above acid (0.205 g) was treated briefly with diazomethane in ether. Isolation of the product in the usual way afforded a quantitative yield of the methyl ester whose physical and spectral characteristics were identical with those of specimen **33** prepared according to method a above. In particular the compound appeared completely homogeneous by tlc analysis.

2-Hydroxy-3-(1-hydroxynonyl)glutaric Acid Di-γ-lactone (35).—A solution of the carbomethoxylated amide **33** (30.45 g) in ether (625 ml) was shaken for 5 min with a solution of "Clorox" (1250 ml, 5.25% NaOCl). The ether layer was washed with water and brine and then dried over magnesium sulfate. Removal of the ether *in vacuo* afforded the oily neutral fraction (14.65 g). A sample of this material was chromatographed over silica gel. Elution of the column with ether–benzene mixtures afforded a solid which after several recrystallizations from hexane–benzene gave pure **36**, mp 78.5–79.5°, whose infrared



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spectrum (neat melt) showed bands at 1808, 1788, and 1740 cm^{-1}. Its nmr spectrum showed absorption at 0.89 [triplet, $(CH_2)_7CH_3$], 1.31 [$(CH_2)_7CH_3$], 2.4–3.4 (multiplet, H_b, H_c, H_d), 3.87 (singlet, OCH_3), and 4.39 ppm (multiplet, H_a). The multiplet for H_b, H_c, and H_d was approximately fitted with a computer, using the following chemical shifts (coupling constants): δ (H_b) 3.25, (H_c) 2.68, (H_d) 3.06 ppm (J_{ab} = 3.5, J_{ac} = J_{ad} = 0, J_{bc} = 1.5, J_{bd} = 9.5, and J_{cd} = −17.0 Hz).

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found: C, 61.23; H, 7.54.

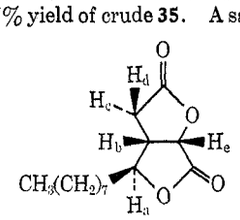
The aqueous phase from the chlorination reaction was acidified with concentrated hydrochloric acid and extracted with methylene chloride. The extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give a very viscous oil (18 g). A sample of this material was crystallized from ethanol to give a pure specimen of **34**, mp 124–125° dec, whose infrared spectrum showed significant bands at 1778, 1757, and 1593 cm^{-1} (Nujol mull) and at 1784 and 1606 in $CHCl_3$. The nmr spectrum showed absorption at 8.67 (broad singlet, CO_2H), 3.50 (multiplet, $-CH_2CH_2N<$), and 1.94 ppm (multiplet, CH_2-$CH_2N<$).

Anal. Calcd for $C_{19}H_{30}ClNO_5$: C, 58.84; H, 7.74; N, 3.61; Cl, 9.16. Found: C, 58.61; H, 7.85; N, 3.47; Cl, 9.14.

The neutral fraction described above was dissolved in dioxane (630 ml) and water (216 ml) containing 48% hydrobromic acid (54 ml). The mixture was refluxed for 48 hr and then concentrated *in vacuo*. The residue was taken up in benzene and refluxed until no more water was collected in a Dean–Stark trap. The benzene solution was extracted with sodium bicarbonate solution (retained) and then after drying ($MgSO_4$) was evaporated to give a neutral oil (4.88 g). An acidic fraction (7.29 g) was obtained from the bicarbonate solution on acidification.

When the crude acidic material **34** was treated with dilute hydrobromic acid in exactly the same way as for the neutral fraction, the yield of identical neutral oil was 7.14 g while an acidic fraction (1.85 g) was obtained from the alkaline wash.

The neutral fractions of these reactions were therefore combined affording a 57% yield of crude **35**. A sample of the material



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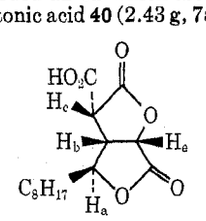
was chromatographed on silica gel and ether–benzene mixtures eluted the pure dilactone in excellent recovery, $n^{24.5}$D 1.4745. Its infrared spectrum (neat) showed bands at 1794, 1782, 1243, 1212, 1146, and 1071 cm^{-1}, while its nmr spectrum displayed absorption at 0.89 [triplet, $(CH_2)_7CH_3$], 1.31 [$(CH_2)_7CH_3$], 2.1–3.3 (multiplet, H_b, H_c, and H_d), 4.34 (multiplet, H_a), and 5.01 ppm (doublet, J = 7.2 Hz, H_e).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.99; H, 8.70.

The acidic materials from these hydrolysis reactions were not investigated in depth.

3-Hydroxy-2-(1-hydroxynonyl)-1,1,3,-propanetricarboxylic Acid 1,3-Di-γ-lactone (40).—The dilactone (**35**, 2.77 g) was added to a 2.6 *M* solution (22 ml) of methyl methoxymagnesium carbonate[21] in dimethylformamide and the mixture heated under a slow stream of dry nitrogen at 120° for 5 hr. The mixture was poured into a mixture of ice cold 6 *N* hydrochloric acid and ether and shaken until all of the precipitated solid had dissolved. The ether phase was washed with water and brine and then dried over magnesium sulfate. Removal of the ether under reduced pressure afforded an oil which after crystallization from hexane gave the dilactonic acid **40** (2.43 g, 75% yield), mp 78–80°.



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Further crystallization did not improve the melting point. Its infrared spectrum showed bands at 1790, 1734, 1288, 1140, and 1075 cm^{-1}, while the nmr spectrum shows, besides the typical characteristics of the C_8H_{17} chain, absorption at ~3.58 (multiplet, H_b), ~3.73 (doublet, J = 5 Hz, H_c), 4.54 (multiplet, H_a), 5.20 (doublet, J = 8 Hz, H_e), and 8.06 ppm (singlet, CO_2H).

Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.57; H, 7.58.

***dl*-Avenaciolide (1).**—Sodium acetate (0.105 g) was dissolved in acetic acid (4 ml) and mixed with a solution of formalin (2.92 ml) and diethylamine (1.00 ml). The dilactonic carboxylic acid (0.295 g) was added to this solution (1 ml) and shaken vigorously until evolution of carbon dioxide ceased (*ca.* 1 min). The mixture was then heated on the steam bath for 5 min, cooled, and poured into water and ether. The ether phase was washed with water, saturated sodium bicarbonate solution, water again, and then dried ($MgSO_4$). Evaporation of the ether afforded a solid, mp 44–51°, which was chromatographed over silica gel. Elution with 5% ether in benzene (v/v) gave *dl*-avenaciolide (0.173 g,

66%), mp 54–57°. Material that had been recrystallized several times from ether–pentane mixtures melted at 55–56°. The infrared spectrum (CCl_4) showed significant bands at 1793, 1662, 1294, 1100, 1061, and 950 cm^{-1} and was identical in all respects with that of the natural material. The nmr spectrum (3% in CCl_4, calibrated) showed absorption at 6.32 (doublet, J = 2.3 Hz), 5.80 (doublet, J = 2.0 Hz), 4.97 (doublet, J = 8.3 Hz), 4.33 (multiplet), 3.57 (multiplet), 1.32, and 0.90 ppm (triplet) [lit.[3] (3% in CCl_4), 6.36 (doublet, J = 2.17 Hz), 4.98 (doublet, J = 8.54 Hz), 4.33 (multiplet), and 3.59 (multiplet)].

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.69; H, 8.26.

The synthetic and natural avenaciolide gave identical thin layer chromatograms on silica gel H being eluted with 20% ether in benzene (v/v).

Registry No.—**1**, 26057-70-5; **7**, 99-11-6; **8**, 6973-55-3; **9**, 39949-60-5; **10**, 39949-61-6; **11**, 39949-62-7; **12**, 39971-68-1; **15**, 39949-63-8; **16**, 39949-64-9; **26**, 39949-65-0; **27**, 39949-66-1; **28**, 39949-67-2; **32**, 39949-68-3; **33**, 39949-69-4; **33** free acid, 39949-70-7; **34**, 39949-71-8; **35**, 39949-88-7; **36**, 39949-89-8; **40**, 39949-90-1; dibenzyl heptylmalonate, 39949-91-2; diethyl heptylmalonate, 607-83-0; benzyl alcohol, 100-51-6; nonanoic anhydride, 1680-36-0; tricarballylic acid, 99-14-9.

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Synthesis of Yohimbines. I. Total Synthesis of Alloyohimbine, α-Yohimbine, and Their Epimers. Revised Structure of Natural Alloyohimbine

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The first total synthesis of alloyohimbine (**6a**) and its isomers **4i**, **4j**, and **8b** has been accomplished. Sodium borohydride reduction of the keto nitrile **3** yielded alcohols **4a** and **4b**, epimeric at C_{17}. The diastereoisomers **4i** and **4j** belonging to the epiallo series were derived from **4a** and **4b**. Epimerization of **4i** at C_3 furnished **6a** which proved to be identical with naturally occurring alloyohimbine except for melting point and optical activity. Compound **6a** could be converted to α-yohimbine under mild conditions, characteristic of those used for epimerization at C_{16}. On the basis of these facts, the structures for alloyohimbine and epialloyohimbine should be revised to **6a** and **4i**, respectively. The hydroxy ester **4j** does not lend itself to facile epimerization at C_3, and has not yet been found in nature.

Two products had been obtained from the catalytic reduction of the unsaturated nitrile ester **1** which had been prepared in the course of the total synthesis of yohimbine.[1] The main product, the trans 2,3-disubstituted nitrile ester, was used for the synthesis of yohimbine. It stood to reason, therefore, to utilize the cis fused isomer **2**, which was the minor product, for the preparation of yohimbines of the allo series, especially so since such bases had not been heretofore synthesized.

The nitrile ester **2** was converted in almost quantitative yield to the pentacyclic ketone **3** using potassium *tert*-butoxide in DMSO. This ketone is strongly enolized both in the solid and dissolved states, and on the basis of its spectral properties must exist mainly in the epiallo-trans (E_t) conformation.[2]

In the course of the earlier sodium borohydride reduction of the analogous ketone nitrile belonging to the normal series, three different nitrile alcohols were isolated out of the theoretically possible four. Under similar conditions (DMF–methanol), **3** furnished only two products, **4a** and **4b**, in a ratio of about 2:3.

From spectral evidence, both **4a** and **4b** must exist in the E_t conformation (Table I). It is also possible to establish the stereochemistry of the C_{17} hydroxyl function from the chemical shift of the C_{17} proton.[3]

(1) Cs. Szántay, L. Töke, and K. Honty, *Tetrahedron Lett.*, 1665 (1965); L. Töke, K. Honty, and Cs. Szántay, *Chem. Ber.*, **102**, 3248 (1969).

(2) (a) W. F. Trager, C. M. Lee, and A. H. Becket, *Tetrahedron*, **23**, 365 (1967). (b) For the meaning of the symbols for the corresponding conformations of yohimban derivatives, see Cs. Szántay, *Magy. Kém. Lapja*, **26**, 490 (1971).

(3) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963).

TABLE I

NMR AND IR DATA

	Nmr,[a] δ		Ir,[b] cm^{-1}	Conformation		
Compd	C_{17} proton multiplet	C_{17} hydroxyl doublet	Bohlmann bands	C_{17} H	C_{17} OH	Skeleton
4a	4.05	5.25	2815, 2775, 2760	e[c]	a	E_t[d]
4b	3.55	5.45	2815, 2775	a[c]	e	E_t
4c	5.15		2815, 2775	e		E_t
4d	4.85		2815, 2780	a		E_t

[a] In DMSO-d_6 at 60 MHz. [b] In pyridine. [c] a = axial, e = equatorial. [d] See ref 2b.

In isomer **4a** the equatorial C_{17} proton is at δ 4.05, while in **4b** the axial C_{17} proton is located higher upfield at δ 3.55. In view of the stable E_t conformation of the two isomers, it follows that the hydroxyl group in **4a** is α while in **4b** it is β. The corresponding O-acylated derivatives **4c** and **4d** were also prepared, and their spectra confirmed the correctness of the C_{17} assignments since the signals for the α protons are now shifted to δ 5.15 and 4.85, respectively. In accordance with the steric assignments, the rate of O-acetylation of **4b** was larger by an order of magnitude than that for the similar reaction of **4a**.

It had been observed in the course of the yohimbine synthesis[1] that the analogs of **4a** and **4b** belonging to the normal series readily epimerized at C-16, bearing the nitrile group, in the presence of aqueous alcoholic alkali at room temperature or under gentle heating. The ΔG value calculated from the equilibrium constants was in good agreement with the energy difference of a