Synthesis of Fatty Acids with Smooth Muscle Stimulant Activity. II. Myristoylbutyrolactones and Analogs[1]

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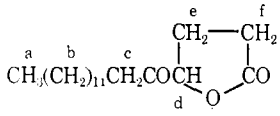
From *Feronia limonia* a compound termed feronolide, mp 115°, has been obtained[2] and the structure **1** was assigned on the basis of chemical evidence and on the presence of a band at 1754 cm^{-1} in the ir spectrum. The location of other bands and the phase or solvent were not reported. The chemical evidence does not exclude the δ-lactone **2**, but this has been described;[3] mp 69°. Feronolide was reported[4] to have spasmogenic



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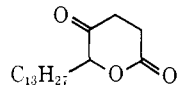

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activity though it does not have the structural features suggested[1] to be common to fatty acids with smooth muscle stimulant action. We therefore undertook synthesis of **1**. 4,5-Dihydroxyoctadecanoic acid γ-lactone[5] was oxidized to give a solid, mp 67–68°. The same ketolactone (**1**) was also obtained in small yield from the reaction of butyrolactone-4-carbonyl chloride[6] with bistridecylcadmium. Our compound (**1**) shows (in CCl_4) two well-resolved peaks at 1805 and 1730 cm^{-1}. Electron-attracting substituents in the γ position of butyrolactone are known[7] to enhance the lactone carbonyl stretching frequency. A mutual enhancement of both C=O stretching frequencies has been observed in compounds containing acetoxyacetyl groupings.[8] The C=O absorption of our compound (**1**) differs considerably in other conditions, being at 1760 and 1715 cm^{-1} in a mull (Nujol) or disk (KCl). This shift on change of phase is greater than the 10–15 cm^{-1} normally encountered.

The nmr spectrum (Table I) of our compound is consistent with the formulation as **1**.

Reduction of this compound (with $NaBH_4$) gave back the hydroxylactone which also shows an enhanced lactone C=O stretching frequency (1790 cm^{-1} in CCl_4) remarkably sensitive to change in state.

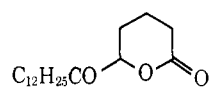
A colloidal suspension of feronolide (10 mg) in $CHCl_3$ (1 ml) and H_2O (9 ml) has been reported[4] to have spasmogenic activity. Compound **1** did not form a stable suspension. Tested in a similar way on isolated guinea pig intestine it showed no effects which were different from those of the solvent mixture. It was soluble in DMF but rapidly precipitated on dilution in an organ bath. No spasmogenic effects were observed.[9]

TABLE I

Chemical shift, τ	No. of protons	Assignment
5.30	1	d
7.2–7.9	6	c, e, f
8.78 and 9.10	25	b and a

We were unable to obtain a sample of feronolide for direct comparison.

Because of the differences between **1** and feronolide, we began synthesis of isomers. 5,6-Dihydroxyoctadecanoic acid[10] was converted to the hydroxy δ-lactone. Oxidation gave a small yield of the ketolactone **3**. This showed some enhancement of C=O stretching frequencies.



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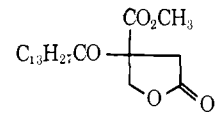

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Methyl 3-oxohexadecanoate[11] was converted to the myristoyl ester (**4**). The corresponding acetyl ester, similarly prepared,[12] was reported to decarboxylate in the course of the reaction. However the myristoyl ester (**4**) proved difficult to decarboxylate, remaining unchanged or cleaving to myristic acid under a variety of conditions. β-Myristoylbutyrolactone was not obtained.

Treatment of methyl 3-oxohexadecanoate[11] with ethylene oxide gave α-myristoylbutyrolactone. This showed no enhancement of the lactone C=O stretching frequency and little alteration on change of state. Tested in the same way as the γ isomer (**1**) it showed no spasmogenic activity.[9]

Experimental Section[13]

4-Hydroxy-5-oxooctadecanoic Acid γ-Lactone (1).—A solution of the hydroxylactone[5] (1.70 g) in Me_2CO (40 ml) was cooled (ice bath) and treated dropwise with 2 *M* H_2CrO_4 (12 ml). The two-phase mixture was stirred for 6 hr while the bath came to room temperature. The acid layer was extracted (Et_2O) and this extract was combined with the residue from evaporation of the Me_2CO, washed (H_2O, 10% $NaHCO_3$), dried ($MgSO_4$), and evaporated to give the crude product (1.56 g) which was treated with charcoal in $CHCl_3$ and recrystallized (petroleum ether, bp 60–80°); yield 1.26 g (75%), mp 66.5–68.5°. *Anal.* Calcd for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88. Found: C, 72.87; H, 10.69. The absorption spectra are discussed above.

The 2,4-dinitrophenylhydrazone had mp 61–63°. *Anal.* ($C_{24}H_{36}N_4O_6$) N.

5,6-Dihydroxyoctadecanoic Acid δ-Lactone.—The dihydroxy

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(13) The compounds described below were all synthesized from either myristic acid (British Drug Houses, 99% by glpc) or 1-bromododecane (Fluka 99.5% by glpc); uv spectra were measured on Unicam S.P. 800; ir spectra on a Perkin-Elmer Model 257; and nmr spectra on a Perkin-Elmer Model R10 (60 Mc). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points are uncorrected.

acid[10] (2.73 g) was heated *in vacuo* at 130° (bath temperature) for 2.5 hr. The product was dissolved in $CHCl_3$, washed (10% $NaHCO_3$), dried ($MgSO_4$), concentrated, and recrystallized (petroleum ether, bp 40–60°); yield 1.18 g (70%), mp 68–69°, ir (CCl_4) 1750 cm^{-1}. *Anal.* ($C_{18}H_{34}O_3$) C, H.

5-Hydroxy-6-oxooctadecanoic Acid δ-Lactone (3).—A solution of *t*-butyl alcohol (986 mg) and CrO_3 (493 mg) in petroleum ether (bp 40–60°) was dried (Na_2SO_4) and treated with a solution of the hydroxylactone (597 mg) in petroleum ether (150 ml). The mixture was allowed to stand in a stoppered flask for 70 hr. It was then kept at reflux for 4 hr, cooled, and treated with H_2O (35 ml) and oxalic acid (*ca.* 0.5 g), then with H_2SO_4 (1 ml) and AcOH (2 ml). The mixture was shaken for 45 min, and the aqueous layer was separated and extracted with petroleum ether. The combined organic solutions were washed (10% $NaHCO_3$, H_2O), dried (Na_2SO_4), and concentrated to give a slowly solidifying brown oil (565 mg), which was recrystallized (petroleum ether, bp 40–60°); yield 25 mg (4%), mp 41–42°; ir (CCl_4) 1760, 1725 cm^{-1}. *Anal.* ($C_{18}H_{32}O_3$) C, H.

Dimethyl Myristoylsuccinate.—A solution of methyl 3-oxohexadecanoate[11] (2.13 g) in MeOH (15 ml) was added to a solution of Na (173 mg) in MeOH (15 ml), stirred at room temperature for 5 hr, and then methyl bromoacetate (1.15 g) was added. Stirring was continued for 30 hr. The mixture was concentrated, diluted with Et_2O, and washed (HCl, H_2O, 10% $NaHCO_3$). The dried (Na_2SO_4) solution was concentrated to give a solid (1.82 g) which was treated with charcoal in CCl_4 and recrystallized (petroleum ether, bp 40–60°); yield 800 mg (30%), mp 46–47.5°, absorption peaks (ir, nmr) as expected. *Anal.* ($C_{20}H_{36}O_5$) C, H.

3-Hydroxymethyl-3-methoxycarbonyl-4-oxoheptadecanoic Acid γ-Lactone (4).—A suspension of the myrisotoylsuccinate (1.07 g) in MeOH (50 ml) was stirred at room temperature for 1 hr with 1 *N* NaOH (3.0 ml). The resulting clear solution was adjusted to pH 9 with 1% H_2SO_4, treated with 10% $NaHCO_3$ (3 ml) and aqueous 40% HCHO (5.0 ml), and stirred at room temperature for 48 hr. The solution was diluted with Et_2O, washed (H_2SO_4, H_2O), dried (Na_2SO_4), and concentrated to give an oil (1.00 g). This was stirred with 25% HCl (35 ml) at room temperature for 45 hr and extracted with Et_2O. The extract was washed (H_2O) until the washings were neutral, concentrated, and heated *in vacuo* at 140° (bath) for 2 hr. The material was reextracted into Et_2O, which was washed (10% $NaHCO_3$), dried (Na_2SO_4), and concentrated to give a semisolid mixture (855 mg), which was recrystallized (petroleum ether, bp 40–60°); yield 40 mg (4%), mp 31–33°, absorption peaks (ir, nmr) as expected. *Anal.* ($C_{20}H_{34}O_5$) C, H.

1-Hydroxy-4-oxoheptadecane-3-carboxylic Acid γ-Lactone.—To a stirred solution at 25° (bath) of Na (952 mg) in EtOH (20 ml) was added a solution of methyl 3-oxohexadecanoate[11] (11.76 g) in EtOH (80 ml). Ethylene oxide (14.56 g) in EtOH (24 ml) was added in eight equal portions at irregular intervals over 90 hr. The reaction mixture was then diluted with Et_2O, washed (1% AcOH, H_2O), dried (Na_2SO_4), concentrated, and recrystallized (petroleum ether, bp 40–60°); yield 4.08 g (35%); mp 48°; ir (CCl_4) 1783, 1727 cm^{-1}; ir (KCl) 1775, 1725 cm^{-1}; nmr (CCl_4) τ 5.59 (m, 2), 6.40 (m, 1), 6.84–8.00 (m, 4), 8.2–9.3 (m, 21). *Anal.* ($C_{18}H_{32}O_3$) C, H.

3-Deoxy Progestins

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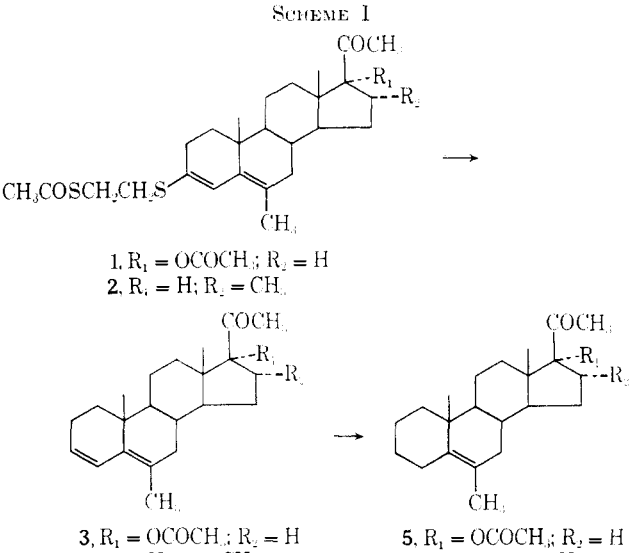
The activation of progesterone by molecular modification, such as introduction of an alkyl group,[1] acetoxy group,[2] halogen atom,[3] and/or unsaturation[4] has achieved success in the hands of a number of investigators. The oral progestational response is enhanced by a factor of as much as 750.[5] These observations had prompted Ringold[6] to suggest "... oxygen function at C-3 ... and acetyl side chain at C-17 positions ... appear to be necessary for high hormonal activity ... (and) steroid receptor interaction ...." The interaction between steroid and protein is well established;[7] in fact, Topper[8] has demonstrated that the *in vitro* effect of progesterone is at an enzymatic locus one step beyond the transferase level.

We were interested in exploring the hypothesis of Ringold[6] regarding the necessity of oxygen function both at C-3 and C-17 (acetyl) to achieve high hormonal activity. We chose 6α-methyl-17α-acetoxyprogesterone and 6α,16α-dimethylprogesterone for our molecular modifications. The progestational activity of the former compound was 40 times that of progesterone,[9] whereas the progestational response of the latter compound was equal to that of progesterone.[10] Deoxylation of the oxygen function in ring A of both these compounds with concurrent alteration of the unsaturation from C-4 to C-5 would certainly decrease their ability to interact with the protein receptor and hence affect their biological response.

The 3-deoxy compounds 17α-acetoxy-6-methylpregn-5-en-20-one (**5**) and 6,16α-dimethylpregn-5-en-20-one (**6**) were synthesized by the procedure outlined in the Experimental Section and as depicted in Scheme I. The

SCHEME I



spectral analyses confirm all structural assignments. The starting materials 3-(β-acetylthioethylthio)-6-metyl-17α-acetoxypregn-3,5-dien-20-one (**1**) and 3-(β-acetylthioethylthio)-6,16α-dimethylpregn-3,5-dien-

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