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 23 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 myristoylsuccinate (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 (33%); 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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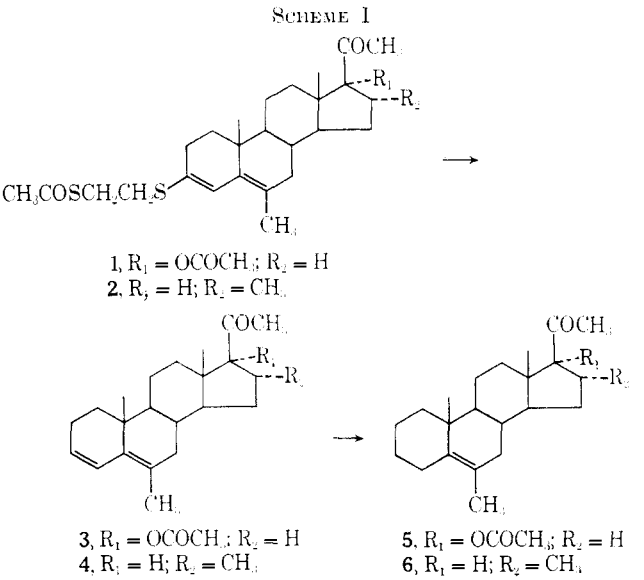
The activation of progesterone by molecular modification, such as introduction of an alkyl group,[1] acetoxy group,[2] halogen atom,[3] and/or unsaturation[4] has achieved success in the hands of a number of investigators. The oral progestational response is enhanced by a factor of as much as 750.[5] 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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20-one (**2**) were prepared by the method of Karmas[11] and Mallory,[12] respectively.

The oral progestational activity of these compounds was determined by the Clauberg test[13] and the endometrial response was scored according to the index of McPhail.[14] The McPhail index for 6α-methyl-17α-acetoxyprogesterone and compounds **5** was found to be +3.0 and +3.2, respectively, at 0.5 mg. These data, though limited in nature, do point out that the oxygen function at C-3 is not an absolute necessity for progestational response. On the other hand the McPhail index of 6α,16α-dimethylprogesterone and the oxime of **6** (2.1 and 0, respectively, at 5.0 mg) points out the importance of the C-20 functional group for protein binding. The polarity of the carbonyl group constitutes a point of contact with the receptor superior to that of the oxime. The oxidation–reduction of the oxygen function at C-3 as a possible factor in the mechanism of action probably can be ruled out.

Experimental Section

All melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. The uv and ir data were obtained on a Cary Mode 111 and Beckman IR-5 spectrophotometers, respectively. Nmr spectra were determined on a Varian A-60 spectrometer in $CDCl_3$ using TMS as an internal standard. Elemental analyses were performed by Midwest Microlab Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

17α-Acetoxy-6-methylpregn-3,5-dien-20-one (**3**).—Raney Ni (88.0 g) was suspended in 800 ml of Me_2CO and refluxed with stirring under N_2 for 0.5 hr. The mixture was cooled to room temperature and to it was added 8.0 g of **1** in 100 ml of THF. Stirring was continued at 25° for 2.5 hr. The reaction mixture was filtered and the filtrate was evaporated to give an oil. Recrystallization from ether–hexane yielded 4.5 g (70%) of **3**: mp 132–133°; λ_{max}^{EtOH} 241 mμ; λ_{max}^{KBr} 1650, 1720, 1731 cm^{-1}; nmr, multiplets at 5.68 and 6.41 ppm (C-3, C-4). *Anal.* ($C_{24}H_{34}O_3$) C, H.

17α-Acetoxy-6-methylpregn-5-en-20-one (**5**).—Compound **3** (1.0 g) was dissolved in 15 ml of AcOH and 700 mg of 5% Pd–C was added. The mixture was hydrogenated at room temperature until 1 equiv of H_2 was consumed. It was filtered and the filtrate was evaporated to give an oil. Repeated recrystallization from hexane gave 250 mg (36%) of **5**: mp 166–168°; $\lambda_{max}^{cyclohexane}$ 198 mμ (ε 8900); λ_{max}^{KBr} 1723, 1737 cm^{-1}; nmr, no resonance due to vinyl protons. *Anal.* ($C_{24}H_{36}O_3$) C, H.

6,16α-Dimethylpregn-3,5-dien-20-one (**4**).—A mixture of 80 g of Raney Ni in 700 ml of Me_2CO was stirred and refluxed for 0.5 hr under N_2. The mixture was cooled to room temperature and to it was added a solution of 6.9 g of **2** in 75 ml of THF. Stirring was continued for 3.5 hr at 25°. The mixture was filtered and the filtrate was evaporated to a dark residue. Chromatographic separation on neutral alumina gave 3.9 g (80%) of **4** on elution with 9:1 hexane–Et_2O. Recrystallization from hexane gave analytically pure sample: mp 125–126°; λ_{max}^{EtOH} 241 mμ; λ_{max}^{KBr} 1650, 1705 cm^{-1}; nmr, 5.30 ppm (vinyl multiplets). *Anal.* ($C_{23}H_{34}O$): C, H.

6,16α-Dimethylpregn-5-en-20-one (**6**).—Compound **4** (500 mg) was dissolved in 15 ml of AcOH and to it was added 250 mg of 5% Pd–C. The mixture was hydrogenated at room temperature until 1 equiv of H_2 was consumed. The mixture was filtered and the filtrate was evaporated to give an oil which failed to crystallize; λ_{max}^{NaCl} 1705 cm^{-1}; nmr, no resonance due to vinyl protons. Analyzed as oxime, mp 75–76°. *Anal.* ($C_{23}H_{37}NO$) C, H, N.

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2-Hydroxy-2-phenylethylhydrazine Monoamine Oxidase Inhibitors

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2-Hydroxy-2-phenylethylhydrazine (**1**) was synthesized first by Benoit[2] and observed to have typical sympathomimetic activity with a potency 1/500th that of epinephrine.[3] Later, Biel, *et al.*,[4] evaluated **1** for monoamine oxidase (MAO) inhibitory activity and found it to be eight times as potent as iproniazid *in vivo*, but inactive at 10^{-5} *M in vitro*. In this study we desired to determine the effect of position and number of carbethoxy groups on MAO inhibitory activity and to verify the lack of *in vitro* activity of **1**.

The N^1-carbethoxy derivative (**2**) was prepared by treating **1**[2] with ethyl chloroformate. The first approach to the synthesis of the N^2-carbethoxy derivative (**3**) involved the reaction of styrene oxide and ethyl carbazate. This procedure led to a complex mixture of products, a situation not unexpected in light of the mixture obtained by treating styrene oxide with ethyl glycinate.[5]

Compound **3** was synthesized by treating styrene bromohydrin with ethyl carbazate. The N^1,N^2-dicarbethoxy derivative (**4**) was prepared from either **2** or **3** by reaction with ethyl chloroformate. That the positions of the carbethoxy groups are correctly assigned to nitrogens and are not on the alcoholic oxygens is shown by the ir absorption of the carbonyl groups of **2**, **3**, and **4**. The carbonyls of ethyl carbazate and diethyl carbonate are at 1716 and 1750 cm^{-1}, respectively. Compounds **2**, **3**, and **4** are at 1690, 1715, and 1725 and 1705 cm^{-1}, respectively. Attempts to cause N → O migration of the carbethoxy group according to the method of Lyle and Durand[6] failed.

Biological Results.—Mitochondrial monoamine oxidase from beef liver was isolated and purified as described by Ho, *et al.*[7] Incubation was carried out at 37° for 30 min in a solution containing 0.15 mμmole of substrate, tyramine-1-C^{14}, per milliliter, varying amounts of inhibitor, 20 μl of enzyme, phosphate buffer pH 7.4, and water to make a final volume of 1 ml. The product, a mixture of *p*-hydroxyphenylacetaldehyde and *p*-hydroxyphenylacetic acid, was extracted with EtOAc in strongly acidic medium. After removal of solvent, the product was assayed for C^{14} in a liquid scintillation spectrometer and the concentration of the inhibitor at which enzyme activity was 50% inhibited (I_{50}) was determined. The results are shown in Table I.

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