analog **4** (n = 2) was less potent than **13** (n = 3) and **16** (n = 4) in protecting mice against the lethal effect of epinephrine.

Monosubstitution in the *ortho* position of the terminal phenoxy nucleus with CH_3 (**5**) did not result in increased potency. Compounds in which the CH_3 was replaced by *o*-CH_3O (**7**) and *m*-CH_3O (**8**) were more effective in the mouse protection test, but **8** was less potent in antagonizing the pressor response of epinephrine and norepinephrine in the anesthetized rat than **7** (Table III). The least active of the monosubstituted phenoxy series was **9** with *p*-CH_3O. In all these compounds n = 2.

Disubstitution with *o*-CH_3 (**6**) or *o*-CH_3O (**10**, **14**) gave compounds of increased potency. In the mouse protection test the 2,6-dimethoxy derivative (**10**, n = 2) was 30 times more potent than the corresponding dimethyl analog **6** (n = 2) and five times more potent than the 2,6-dimethoxy compound **14** (n = 3).

As a result of this preliminary investigation the hypotensive compound **10** [2-(2,6-dimethoxyphenoxy)ethylaminomethyl-1,4-benzodioxane] and the CNS depressant **2** [2-(3,6-dioxaheptyl)aminomethyl-1,4-benzodioxane] were selected for further study and the results will be published later.

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The Synthesis of 3,11β,17α-Trihydroxy-19-norpregna-1,3,5(10)-trien-20-one

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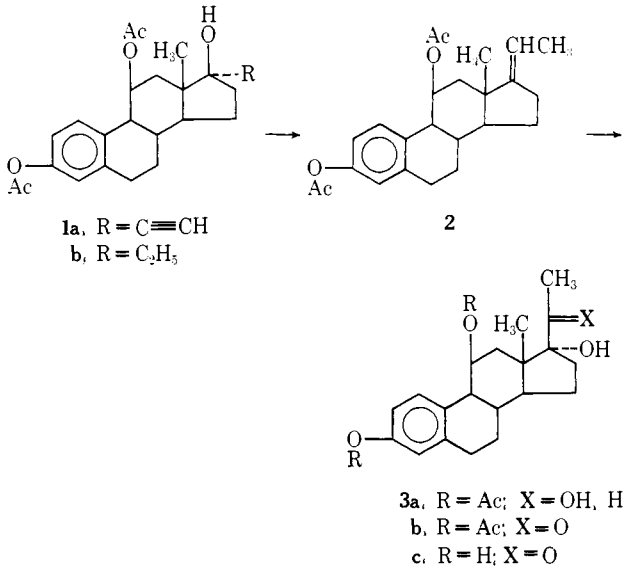
In order to examine the hormonal properties of some 3,20-bisoxygenated 19-norpregna-1,3,5(10)-trienes, the synthesis of 3,11β,17α-trihydroxy-19-norpregna-1,3,5-(10)-trien-20-one (**3c**) was undertaken. This substance, previously available only by microbiological fermentation,[1] was prepared in a synthesis beginning with the diacetate **1a**, obtained by hydrogenation of the readily available 11β-hydroxy-17α-ethynylestradiol.[2] The hydrogenated product **1b** was dehydrated with $SOCl_2$ and pyridine to **2** and then oxidized with OsO_4 in pyridine[3] to the diol **3a** (Scheme I). Oxidation of the diol **3a** with CrO_3 in the presence of $MnCl_2$[4] gave the ketone **3b** which was hydrolyzed to **3c**. The ORD curve of **3c**, which exhibits a positive Cotton effect, establishes the 17β configuration of the acetyl group.

Biology.—The pregnatriene **3c** exhibited antiinflammatory activity in the cotton granuloma assay[5] at 25 mg when administered by injection and no activity at 5 mg when administered orally. When tested for its estrogenic activity by injection using estrone as a standard in the mouse uterine-growth assay,[6] it was active at 0.1 mg and, when tested for antiandrogenic activity[7] at 5 mg by injection, the substance exhibited no activity.

SCHEME I



Experimental Section[8]

3,11β-Diacetoxy-17α-ethynylestra-1,3,5(10)-trien-17β-ol (1a).—When 2.2 g of 11β-hydroxyethynylestradiol[2] was acylated with Ac_2O and pyridine for 24 hr at 25°, 2.0 g of crude **1a** was obtained. Crystallization of the crude product from Et_2O gave an analytical sample, mp 160–163°, $[\alpha]^{25}D$ −9° ($CHCl_3$). *Anal.* ($C_{24}H_{28}O_5$) C, H.

3,11β-Diacetoxy-17α-ethylestra-1,3,5(10)-trien-17β-ol (1b).—When 15.5 g of **1a** was hydrogenated in 250 ml of EtOAc in the presence 1.5 g of 5% Pd–C at atmospheric pressure, 16 g of crude **1b** was obtained. Crystallization of the crude product (Me_2CO) and hexane gave an analytical sample, mp 195–196°, $[\alpha]D$ +53.5° ($CHCl_3$). *Anal.* ($C_{24}H_{32}O_5$) C, H.

3,11β-Diacetoxy-19-norpregna-1,3,5(10),17(20)-tetraene (2).—A solution of 15.3 g of **1b** in 120 ml of pyridine was added dropwise, with stirring over 30 min, to a solution of 8.6 g of $SOCl_2$ in 75 ml of pyridine maintained at −15°. The solution was allowed to come to 20°, then cooled to 0°, diluted with 5 ml of EtOH and 2.2 l. of $CHCl_3$, and stirred. The $CHCl_3$ solution was washed with three 300-ml portions of H_2O and 300 ml of aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. Since some hydrolysis at the C-3 acetate occurred, the crude product was dissolved in 30 ml of pyridine and 15 ml of Ac_2O. After 30 min ice and H_2O were added to the solution. Trituration at 0° yielded a crystalline material which was collected by filtration. The crude product, mp 118–123°, weighed 12.3 g. Crystallization of the crude product from CH_2Cl_2 and MeOH gave an analytical sample: mp 147–150°; nmr maxima at 54 (C-13 methyl), 89 and 96 (C-20 methyl), and 303 (multiplet, C-20 H) cps; $[\alpha]^{25}D$ +54° ($CHCl_3$). *Anal.* ($C_{24}H_{30}O_4$) C, H.

3,11β-Diacetoxy-17α-hydroxy-19-norpregna-1,3,5(10)-trien-20-one.—A solution of 12.6 g of crude **2** in 75 ml of pyridine was mixed with a solution of 8.4 g of OsO_4 in 50 ml of pyridine and allowed to stand for 18 hr. To the solution was then added with

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(8) The authors wish to thank Dr. R. T. Dillon and staff for the analyses, spectra, and rotations, and Mr. R. Dahm and staff for the chromatography reported. The nmr spectra were determined in $CDCl_3$ on a Varian Model A-60 spectrometer at 60 Mc with Me_4Si as an internal standard. The melting points are corrected.

stirring a solution of 14.9 g of $NaHSO_3$, 251 ml of H_2O, and 166 ml of pyridine. After 15 min the solution was extracted twice with $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$) and distilled to dryness. Slow evaporation and trituration of an Et_2O–C_6H_{14} solution of the residue gave 7.45 g of crude diol: mp 110–125°; nmr maxima at 58 (C-13 Me) and 68 and 74.5 (C-21 Me) cps. A solution of 6.6 g of the crude diol **3a** in 100 ml of DMF was added with stirring to a cold solution of 35.6 ml of 8 *N* CrO_3–H_2SO_4, 4.7 g of $MnCl_2$, and 78 ml of DMF. The solution was stirred for 2.5 hr at 20° and then added while stirring vigorously to 2.2 l. of ice and H_2O. The crude product which was collected by filtration and dried, weighed 5.3 g. The crude product was dissolved in C_6H_6 and purified by column chromatography on 450 g of silica gel (Davison 60–200 mesh). Elution of the column with C_6H_6–EtOAc (9:1) gave 1.3 g of **3b**, mp 147–148°. Crystallization of the crude product (Et_2O) gave an analytical sample: mp 149–151°; nmr maxima at 53 (C-13 methyl), 110 and 137 (9H, C-3, C-11, and C-20 acetyl) cps. *Anal.* ($C_{23}H_{30}O_6$) C, H.

3,11β-Trihydroxy-19-norpregna-1,3,5(10)-trien-20-one (3c).—To a solution of 900 mg of crude **3b** in 100 ml of MeOH was added with stirring a solution of 500 mg of KOH in 20 ml of 50% aqueous MeOH. The solution was warmed and 50 ml of H_2O was added. The MeOH was removed by distillation and the solution was refluxed under N_2 for 5 hr, cooled, and acidified at 0° with AcOH. The product, which was collected by filtration, washed (H_2O), and dried, weighed 620 mg. Crystallization of the crude product (Me_2CO and hexane) gave an analytical sample: mp 237–240°; λ_{max} (KBr) 2.82, 2.99, 5.82, and 6.17 μ. The ORD curve of **3c** in MeOH exhibited a broad peak at 330 mμ (Φ 1122) and a trough at 295 mμ (Φ 900). *Anal.* ($C_{20}H_{28}O_4$) C, H.

Barbiturates. Structural Comparisons. I. Amobarbital, Methylamobarbital, and Butethal[1]

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Recently a quantitative study has been made concerning the structure-activity relationships of the barbiturates.[2,3] It has been suggested that the partition coefficients and the rate of metabolism play an important role in the duration of action and potency of the barbiturates.[3] With reference to the metabolic inactivation of barbiturates, it has been shown that the ω − 1 carbon of the side chain of barbiturates undergoes preferential oxidation in many cases. In several barbiturates studied,[4] the ω − 1 carbon turned out to be the 3- or γ-carbon atom. In order to differentiate between the γ carbon or ω − 1 carbon as to the susceptibility toward oxidation, Maynert[5] studied the metabolism of 5-ethyl-5-*n*-hexylbarbituric acid in dogs and found the ω − 1 carbon and not the γ carbon most susceptible to metabolic oxidation.

With this in mind, it was decided to study compounds without C–H bonds at the ω − 1 carbon. If the ω − 1 carbon does not possess a C–H bond, that carbon will not be susceptible to oxidation and one would expect a longer acting and more potent compound. The compounds chosen for the first comparison were 5-ethyl-5-(3-methylbutyl)barbituric acid (amobarbital, I), 5-ethyl-5-(3,3-dimethylbutyl)barbituric acid (methylamobarbital, II), and 5-ethyl-5-*n*-butylbarbituric acid (butethal, III). Comparison of the substituents on the ω − 1 carbon for I and II should give a good estimate of the difference between a very easily oxidized ω − 1 C–H bond as in I (forms a tertiary free radical)[6] against a carbon containing no ω − 1 C–H bonds for oxidation as in II. The pharmacological studies performed show that II is a more potent and a longer acting compound than I or butethal.

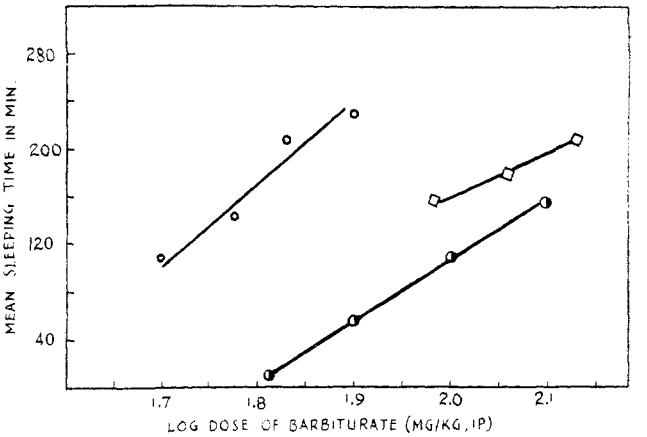
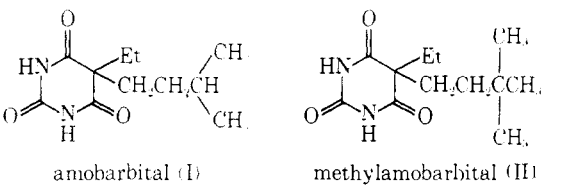
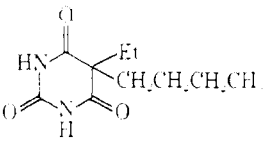


Figure 1.—Log dose–response (duration of action) curves of amobarbital (AMB·Na) (●—●), butethal (BUT·Na) (◇—◇), and methylamobarbital (CH_3AMB) (○—○) in male mice. Each point represents the value obtained from ten animals.


amobarbital (I)

methylamobarbital (II)


butethal (III)

Pharmacological Studies.—Figure 1 shows the relationship between dose and the duration of action of amobarbital, butethal, and methylamobarbital in mice. It can be readily seen that amobarbital is shorter acting than methylamobarbital. Comparisons at 120 min show methylamobarbital to be 1.9 times as active as amobarbital when compared on an equimolar basis.

In order to relate this difference in activity to the differences in metabolic inactivation, the oxidative enzymes (liver) were blocked by using β-diethylaminoethyl diphenylpropylacetate and iproniazid.[7,8] The results are shown in Figures 2 and 3. Figure 2

(1) This work was supported by Grant FR-05455 from the National Institutes of Health.

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(6) Amobarbital can be hydroxylated at the ω-1 carbon atom by chromic acid oxidation under very mild conditions; see ref 4b.

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