1.7 g. of chloranil in 65 ml. of refluxing isobutyl alcohol for 10 hr. Work up gave 2.3 g. of a yellow oil which was chromatographed on 200 g. of Florisil. Ethyl acetate–benzene (2% and 5%) fractions eluted the product as yellow crystals (1.358 g.), m.p. 181–184° (from ether). The analytical sample had m.p. 183–185°, $[\alpha]^{23}D$ +52° (1%, $CHCl_3$) $\lambda_{max}$ 294 mμ ε 23,400.

**17α-Ethyl-6-dehydroprogesterone (IVb).**—A quantity of 3.985 g. of 17α-ethylpregnenolone (IIb) was dissolved in 160 ml. of toluene. Part of the solvent (35 ml.) was distilled and 35 ml. of cyclohexanone, 3.9 g. of aluminum isopropoxide and 3.9 g. of chloranil were added. The mixture was refluxed for 1 hr. Work up gave 3.768 g. of anamorphous material, which was chromatographed on 110 g. of alumina (Woelm III). The petroleum ether–benzene (1:1) fractions contained IVb. A sample was purified for analysis through thick layer chromatography (system: $CCl_4$–EtOAc, 4:1), m.p. 170–173°, $[\alpha]^{23}D$ +48.5° (1%, $CHCl_3$), $\lambda_{max}$ 287 mμ ε 25,900.

*Anal.* Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.10; H, 9.31.

**6-Chloro-17α-ethyl-6-dehydroprogesterone (IVc).**—To a quantity of 1.98 g. of the 6-dehydro compound IVb dissolved in 50 ml. of dry methylene chloride was added 95 ml. of a 0.364 *N* solution of monoperphthalic acid in ether. After 65 hr. the mixture was washed with sodium bicarbonate solution and water to give 1.945 g. of a partly crystalline residue. Some starting material was shown to be present by thin layer chromatography. Crystallization from ether gave 675 mg. of 6α,7α-epoxide, m.p. 215–228° dec. Without purification, this epoxide was dissolved in 25 ml. of acetic acid and the solution saturated with dry hydrochloric acid for 5 min., then left at room temperature for 16 hr.[41] Extraction with ether and washing to neutrality gave, after evaporation, 0.690 g. of a yellow oil which crystallized from ether to give 0.284 g. of IV as needles, m.p. 172–175°. A sample was recrystallized for analysis, m.p. 177–179°, $[\alpha]^{23}D$ +30.9° (1%, $CHCl_3$), $\lambda_{max}$ 288 mμ ε 24,800.

*Anal.* Calcd. for $C_{23}H_{31}ClO_2$: C, 73.68; H, 8.33; Cl, 9.45. Found: C, 73.87; H, 8.67; Cl, 9.28.

**6,17-Dimethyl-6-dehydroprogesterone (IVd).**—6,17-Dimethylpregnenolone (IIe) (2.35 g.) was dissolved in 120 ml. of toluene and 24 ml. of distilled cyclohexanone. Part of the solvent (30 ml.) was distilled to remove traces of water. Aluminum isopropoxide (2.4 g.) and 2.4 g. of chloranil were added, and the mixture was stirred and refluxed for 1 hr. It was diluted with ether and washed with 5% sodium hydroxide solution until colorless washings were obtained, then with water. The organic layer was evaporated, then steam distilled to remove the excess cyclohexanone. A slightly yellow residue (2 g.) was obtained which was purified on a column of alumina (Woelm III). Petroleum ether–benzene (4:1 and 1:1) eluted crystalline fractions (1.283 g.) which were recrystallized from ether to give 0.813 g. of IVd, m.p. 144–146°, identical with an authentic sample.[32]

(41) L. H. Knox, J. A. Zderic, J. P. Rimlas, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **82**, 1230 (1960).

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# Some 3-Phenyl Derivatives of Pregnane-11,20-dione

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The addition of phenylmagnesium bromide to pregnane-3,11,20-trione 20-ethylene ketal (III) yielded both epimeric alcohols, which were separated and characterized. After removal of the protective ketal, a series of 3-phenyl substituted pregnane-11,20-diones was prepared, none of which showed any aldosterone antagonist activity.

The observation that steroids possessing a spirolactone function at C-17 are able to inhibit competitively[1] the mineral-corticoid activity of aldosterone revealed an entirely new field of pharmacological interest. However, in the interval since the original disclosures,[2] no clinically useful activity-enhancing groups have been found although much work has been expended in that direction.[3] This disappointing phenomenon has provided the impetus for a search for other compounds also capable of exerting the same biological function.

The proposition that lactones are uniquely capable of inhibiting the action of aldosterone seems untenable, *e.g.*, this activity is also well documented for progesterone.[4] In addition a low order of activity has been claimed for numerous other steroids.[5] Accordingly, the possibility that the activity of a derivative other than a lactone might be enhanced by the application of classical antimetabolite concepts[6] was examined. In particular, it was felt that increasing the "back-side bulk" of progesterone might lead to an interesting aldosterone antagonist. The synthesis of such a compound, 3α-phenyl-3β-hydroxypregnane-11,20-dione (Va) is the subject of this paper.

The acid-catalyzed reaction of ethylene glycol with 3α-acetoxypregnane-11,20-dione resulted in hydrolysis of the acetate functionality as well as ketal formation to give the previously described II.[7] Oxidation readily afforded the desired substrate (III) for the addition of phenylmagnesium bromide. As expected, the

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action of phenylmagnesium bromide on III gave two products which were separated readily by chromatography. In addition to biphenyl, two isomeric compounds which gave correct analyses for the desired IV were isolated. The first product to be eluted from the column was assigned the structure IVa on the basis of its polarity,[8] lesser yield[9] and more positive rotation.[10]

Dioxolane removal with *p*-toluenesulfonic acid in acetone of *either* of the two isomers afforded a mixture of a dehydration product and the *same* alcohol. This alcohol was also obtained by the action of aqueous acetic acid at room temperature on IVa and hence was assigned the structure Va. The isomeric alcohol (Vb) was obtained by treating IVb under identical conditions although a small amount of Va was also obtained. The olefin (VI) was prepared by the methanesulfonyl chloride–pyridine dehydration of Va and assigned the 3-dehydro structure on the basis of the greater stability of the 3-double bond in the pregnane series.[11] The isolation of only one alcohol (Va), as well as the unsaturated compound (VI), under strongly acidic conditions and the isolation of Va as well as Vb from the acetic acid reversal of IVb strongly suggest an easy dehydration of the equatorial hydroxyl in these 3-phenyl substituted compounds and rehydration to the thermodynamically more stable equatorial phenyl isomer (Va). Since dehydration of the axial hydroxyl and rehydration would give Va also, nothing is learned about the relative ease of dehydration of axial and equatorial hydroxy groups in this series. Alternatively, the invocation of an intermediate benzylic carbonium ion would reasonably rationalize the formation of these products.

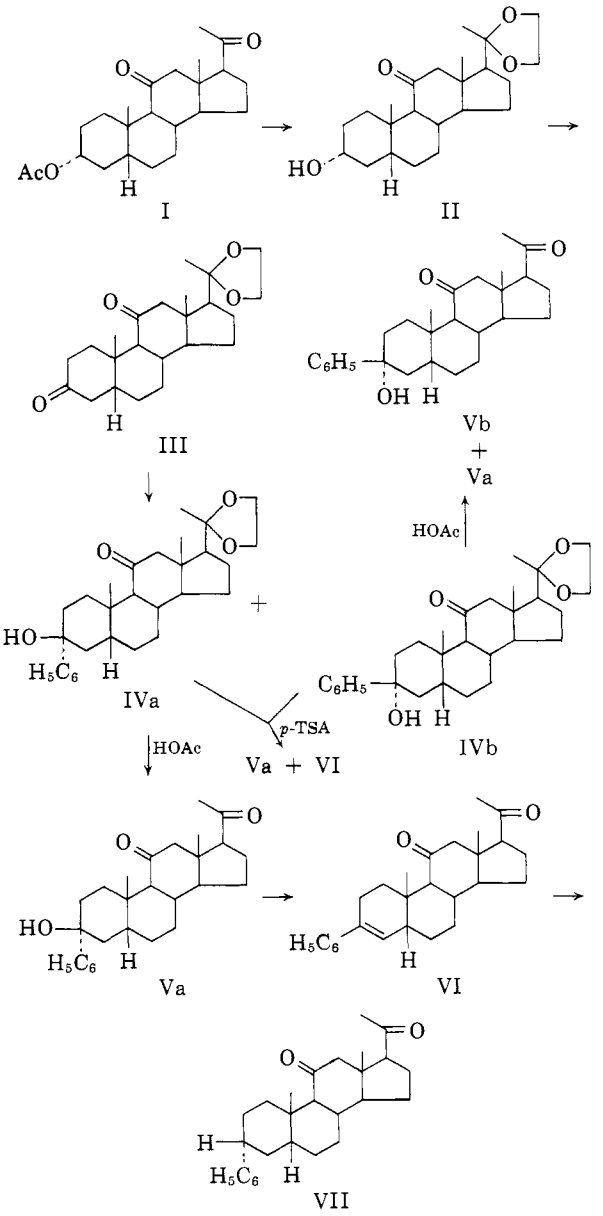
Further support for the structural assignments at C-3 is based on the differential shielding experienced by the 19-methyl group (see Table I). Since increased or decreased shielding effects occur whenever groups face or lie within the plane of a nearby aromatic ring, respectively, one would expect the former condition to be more nearly fulfilled by the 3$\beta$-phenyl in Vb (relative to 3$\alpha$-hydroxypregnane-11, 20-dione). Conversely, the atypically low field position of the 19-methyl in Va favors the 3$\alpha$-phenyl assignment.

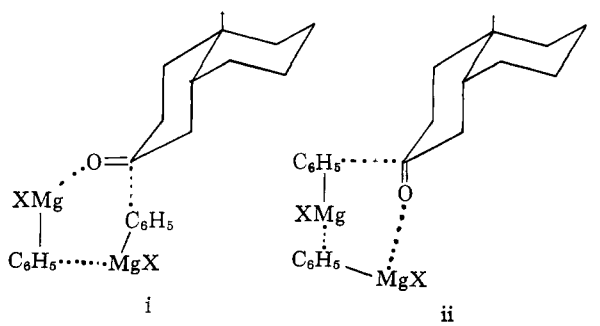
TABLE I[12]

| Compound | 19-$CH_3$ | 18-$CH_3$ | $CH_3CO$ |
|---|---|---|---|
| Va | 8.73 | 9.39 | 7.90 |
| Vb | 8.92 | 9.40 | 7.91 |
| 3$\alpha$-Hydroxypregnane-11,20-dione | 8.84 | 9.40 | 7.90 |

Hydrogenation of VI afforded a reaction product of wide melting point range, but only one product could be isolated by crystallization. The added hydrogen at C-3 is assumed to have the $\beta$-configuration since VI could be adsorbed on a large surface only on the $\beta$-side.

Neither Va or Vb showed significant activity as an aldosterone antagonist at a dose of 10.7 mg./kg./rat in the DOCA-loaded, adrenalectomized rat.[13]

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(9) Observation of molecular models would lead one to expect that the Grignard intermediate (ii) (see F. C. Whitmore, paper presented before the Atlantic City meeting of the American Chemical Society, September, 1941) would predominate over i by virtue of the bad interaction with the 7$\alpha$ and 9$\alpha$-hydrogens in i and hence IVb would be the major product. This interaction appears to be *greater* than that of the 1,5$\beta$ hydrogens in ii.

(10) A. K. Bose and B. G. Chatterjee, *J. Org. Chem.*, **23**, 1425 (1958). However, it should be realized that the unsaturation of the phenyl group adjacent to the asymmetric center may have a profound effect on the rotation, thus vitiating these conclusions.

(11) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 276. The presence of the 3-phenyl group, however, might result in a different order of stability and so this assignment should be regarded as tentative.

(12) The n.m.r. spectra were obtained with a Varian V-4300G high resolution spectrometer operating at 60 megacycles. The chemical shifts are reported as tau ($\tau$) values. We would like to thank Dr. N. R. Trenner and Mr. B. H. Arison for making these determinations.

(13) We are indebted to Dr. M. Glitzer and his associates of the Merck Institute for Therapeutic Research, Rahway, N. J., for these evaluations (unpublished procedure of Drs. Glitzer and S. L. Steelman).

## Experimental[14]

**3α-Hydroxypregnane-11,20-dione 20-Ethylene Ketal (II).**—Twenty grams (0.0534 mole) of 3α-hydroxypregnane-11,20-dione acetate (I) was suspended in a mixture of 1 l. of ethylene glycol and 3.2 g. of *p*-toluenesulfonic acid monohydrate. The mixture was slowly distilled (total time of distillation, 4 hr.) under water pump vacuum until 800 ml. of distillate was collected. The reaction mixture was neutralized with anhydrous pyridine, poured into benzene and washed with water. The aqueous layer was re-extracted with benzene and the combined benzene layers were washed 3 times with water, dried and concentrated *in vacuo*. The oil crystallized from ether–petroleum ether to give 15.78 g. of crude II. This material was recrystallized to give 12.2 g. (61%) of II, melting at 148.5–153.5° (lit.[7] m.p. 143–145°).

**Pregnane-3,11,20-trione 20-Ethylene Ketal (III).**—A solution of 3α-hydroxy-11,20-dione 20-ethylene ketal (3.0 g., 0.0080 mole) in 30 ml. of dry pyridine was added to a cold, stirred mixture of oxidizing reagent prepared by adding 3 g. of chromium trioxide in small portions with vigorous stirring to 30 ml. of anhydrous pyridine at 0–5°. The reaction mixture was stirred until solution was effected and then allowed to stand at room temperature overnight. After the solution was poured into ice-water, it was extracted several times with ether. The extracts were washed several times with water, dried and concentrated *in vacuo*. The product crystallized from ether to yield 1.9 g. (64%) of III; m.p. 148.5–150.5°, $[\alpha]^{24}D$ +60.5° (*c*, 1.003, $CHCl_3$).

*Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.38; H, 9.22.

**3α-Hydroxy-3β-phenyl-(IVa) and 3β-Hydroxy-3α-phenylpregnan-11,20-dione 20-Ethylene Ketal (IVb).**—A warm solution of pregnane-3,11,20-trione 20-ethylene ketal (0.500 g., 0.00134 mole) in 30 ml. of anhydrous ether was added over a 30 min. period to a stirred ethereal solution of phenylmagnesium bromide (0.0113 mole in 30 ml.). The reaction mixture was heated under reflux and stirred for 2 hr. The excess Grignard reagent was decomposed with saturated ammonium chloride solution and the mixture was extracted with a benzene:ether mixture. The extracts were washed with water, dried and concentrated *in vacuo* to yield 0.90 g. of an oil. This oil was adsorbed on a column of 36 g. of neutral alumina using 3:1 petroleum ether:ether. Biphenyl and bromobenzene were eluted using this solvent. The first steroidal fractions to be eluted by 1:1 petroleum ether:ether were combined and crystallized from ether:petroleum ether to give IVa (0.105 g., 17%), m.p. 160.5–163.5°. The analytical sample was recrystallized from the same solvent: m.p. 163.5–165.5°, $[\alpha]^{24}_{546}$ +85° (*c*, 0.528, $CHCl_3$).

*Anal.* Calcd. for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 77.17; H, 8.67.

The latter fractions were crystallized from ether:petroleum ether to give IVb (0.205 g., 34%), m.p. 199.5–202.5°. The analytical sample was recrystallized from the same solvent: m.p. 202.5–203.5°, $[\alpha]^{24}_{547}$ +63° (*c*, 0.514, $CHCl_3$).

*Anal.* Calcd. for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 76.86; H, 8.70. Intermediate fractions (0.225 g.) contained mostly IVb by infrared analysis.

**3β-Hydroxy-3α-phenylpregnane-11,20-done (Va).**—A solution of 784 mg. (0.00173 mole) of 3β-hydroxy-3α-phenylpregnane-11,20-dione 20-ethylene ketal (IVa) in 20 ml. of 90% acetic acid was allowed to stand at room temperature overnight. After neutralizing the reaction mixture with a saturated sodium bicarbonate solution, the resultant precipitate was filtered, washed well with water and dried; weight, 660 mg. The product was crystallized from ether:petroleum ether: 571 mg. (81%), m.p. 197.5–200.5°, $[\alpha]^{24}D$ +111.0 (*c*, 0.519, $CHCl_3$).

*Anal.* Calcd. for $C_{27}H_{36}O_3 \cdot H_2O$: C, 76.02; H, 8.98. Found: C, 76.11; H, 8.64.

**3α-Hydroxy-3β-phenylpregnane-11,20-dione (Vb).**—A solution of 1.224 g. (0.00271 mole) of 3α-hydroxy-3β-phenylpregnane-11,20-dione 20-ethylene ketal in 31 ml. of 90% acetic acid was allowed to stand at room temperature overnight and then worked up in an identical manner as in the preparation of Va. The total crude (1.1 g.) was adsorbed on 40 g. of neutral alumina and eluted with ether. The early fractions (325 mg.) were crystallized from ether:petroleum ether and proved to be identical with Va; yield, 265 mg. (24%), m.p. 195.5–199.5°. The later fractions (700 mg.) also were crystallized from ether:petroleum ether: 445 mg. (40%), m.p. 177.5–178.5°, $[\alpha]^{24}D$ +92.6° (*c*, 1.007, $CHCl_3$).

*Anal.* Calcd. for $C_{27}H_{36}O_3 \cdot C_5H_{12}O$: C, 78.11; H, 8.46. Found: C, 78.19; H, 8.62.

**Strongly Acidic Reversal of IVa and b.**—These *p*-toluenesulfonic acid catalyzed reversals resulted in essentially the *same* mixture of products in the same proportion. For this reason only the reaction of IVb is described.

A solution of 336 mg. (0.00745 mole) of 3α-hydroxy-3β-phenylpregnane-11,20-dione 20-ethylene ketal and 20 mg. of *p*-toluenesulfonic acid monohydrate in 5 ml. of acetone was allowed to stand at room temperature overnight. The reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with water, dried and concentrated *in vacuo*. The resultant oil was adsorbed on 12 g. of neutral alumina with 2:1 petroleum ether:ether. 3-Phenyl-3-pregnene-11,20-dione was eluted with 1:1 petroleum ether:ether and crystallized from cold petroleum ether: 150 mg. (52%), m.p. 118.5–120.5°, $[\alpha]^{24}D$ −174° (*c*, 1.022, $CHCl_3$); $\lambda^{MeOH}_{max}$ 249 mμ (*E* = 12,400).

*Anal.* Calcd. for $C_{27}H_{34}O_2$: C, 83.03; H, 8.78. Found: C, 82.58; H, 8.87.

The latter fractions contained 3β-hydroxy-3α-phenylpregnane-11,20-dione (Va), 110 mg. (36%), m.p. 193.5–196.5° (undepressed with authentic Va). Va was found in the hydrolysis of either IVa or b.

**3-Phenyl-3-pregnene-11,20-dione (VI).**—A solution of 3β-hydroxy-3α-phenylpregnane-11,20-dione (400 mg., 0.00098 mole) in 2.5 ml. of anhydrous dimethylformamide, 1.0 ml. of dry pyridine and 0.5 ml. of methanesulfonyl chloride was heated at 75° for 1 hr. The reaction mixture was diluted with water and the solid collected and dried. The product was adsorbed on neutral alumina and eluted with 3:1 petroleum ether:ether, yield, 294 mg. (77%), m.p. 110.5–114.5°.

**Hydrogenation of VI.**—A solution of 3-phenyl-3-pregnene-11,20-dione (200 mg., 0.000512 mole) in 17.0 ml. of methanol was hydrogenated using platinum oxide as the catalyst (hydrogen uptake 95%). Concentration of the filtered solution gave 200 mg. of material melting at 192.5–217.5°. A small amount could be recrystallized to constant melting point from MeOH:$Et_2O$; m.p. 223–225°, $[\alpha]^{25}D$ +135° (*c*, 1.019, $CHCl_3$).

*Anal.* Calcd. for $C_{27}H_{36}O_2$: C, 82.60; H, 9.24. Found: C, 82.92; H, 9.19. Comparison of the infrared spectra of both products would indicate that VI probably was the major product of the hydrogenation.

(14) All melting points were taken on a Kofler micro-hot stage and are corrected. We would like to thank Mr. R. N. Boos and associates for microanalyses.