benzene and 30 ml. of ether, was washed successively with 10% sodium bicarbonate, 10% sodium hydroxide, water, 5% sulfuric acid and water. Evaporation of solvent yielded 95 mg. of yellow oil which, on chromatography as described above for (a), gave 45 mg. of XIIa, λ_{max} 241 mμ, log ε 4.11, infrared spectrum identical with the product obtained above.

(d) By Inversion of 19-Nor-6β-methyltestosterone Acetate.—A slow stream of dry hydrogen chloride was passed for 45 minutes through a solution of 40 mg. of IXb in 20 ml. of dry chloroform held at 0 to −5°. The acid then was removed by a stream of nitrogen and the chloroform solution washed to neutrality with water and finally evaporated. The oily residue was reacetylated and the product crystallized from aqueous methanol to yield XIIb, m.p. 118–120°, identical with the product obtained in (a).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. CXXV.[1] The Synthesis of 6-Phenyl Hormone Analogs

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When 5α,6α-oxidoprogesterone-3,20-biscycloethylene ketal is treated with phenylmagnesium bromide the corresponding 6β,5α-phenylhydrin is produced in high yield. Ketal hydrolysis of this fission product followed by dehydration of the 5α-hydroxyl group then leads to 6β-phenylprogesterone which may be epimerized to 6α-phenylprogesterone. The synthesis of 6α-phenyl-17α-hydroxyprogesterone by a similar reaction sequence is also described. While 5α,6α-oxidocortisone biscycloethylene ketal also provides its phenylhydrin in high yield, no satisfactory method for its conversion to 6α-phenylcortisone was found.

The literature contains numerous examples[2] of epoxide openings with arylmagnesium bromides. This knowledge combined with the fact that the steroid 5α,6α-epoxide is so labile toward methylmagnesium bromide[3] made the use of phenylmagnesium bromide appear attractive as a method for introducing the phenyl group in the C-6 position.[4]

Thus when 5α,6α-oxidoprogesterone biscycloethylene ketal (Ia) was treated for five hours with a large excess of phenylmagnesium bromide in boiling tetrahydrofuran the epoxide was smoothly opened to afford in 80% yield the corresponding 6β-phenyl-5α-hydroxy compound (IIa). Support for the structure of IIa in addition to its elemental analysis was found in the low intensity maxima which it exhibited at 254 and 260 mμ in the ultraviolet and also by bands at 2.83 (hydroxyl), 6.26, 13.26 and 14.34 μ in the infrared.[5]

When II was allowed to stand for one hour at room temperature in acetic acid containing a few drops of hydrochloric acid, hydrolysis of the ethylene ketal groups was effected thus providing the phenylhydrin-3,20-dione (IIIa) in 65% yield after chromatography. This yield was raised to 80% when the tetrahydrofuran–perchloric acid method[6] was employed. Thionyl chloride dehydration of III in pyridine then led to 6β-phenylprogesterone (IV) whose structure followed from its ultraviolet spectrum, λ_{max}^{EtOH} 242 mμ, log ε 4.14, and conversion to the more stable equatorial 6α-phenylprogesterone (Va) under alkaline epimerizing conditions. Alternatively the 6α-phenyl epimer Va could be obtained directly from the phenylhydrin-3,20-dione (IIIa) by the action of dilute methanolic potassium hydroxide at room temperature overnight.

Comparison of the optical rotatory dispersion curves for the two C-6 epimers does not disclose any striking differences between them as would be expected on the basis of all C-6 epimeric pairs previously examined. In the case of the α-phenyl isomer as compared to progesterone one observes an intense lowering of the peak in the 310 mμ region which may be due to an electronic effect and/or the relatively large bulk of the phenyl group.[7]

Employing a similar set of reactions 6α-phenyl-17α-hydroxyprogesterone (Vb) also was prepared and the relevant details can be found in the Experimental section.

In the case of 5α,6α-oxidocortisone biscycloethylene ketal acetate (VI)[8] the epoxide opening was equally efficacious in producing the corresponding phenylhydrin VII. Upon treatment of VII with perchloric acid in tetrahydrofuran[6] selective hydrolysis of the 3-cycloethylene ketal group resulted to yield the phenylhydrin-3-one (VIII) which after standing overnight with dilute alkali was converted to 6α-phenylcortisone-20-cycloethylene ketal (IX). When IX was treated under conditions known to effect hydrolysis of 20-cycloethylene ketals[9] the resulting non-crystalline product, λ_{max}^{EtOH} 236–238 mμ, log

(1) Paper CXXIV, A. Bowers, E. Denot, M. B. Sánchez, M. Sánchez Hidalgo and H. J. Ringold, THIS JOURNAL, **81**, in press (1959).

(2) See N. G. Gaylord and E. I. Becker, *J. Org. Chem.*, **15**, 305 (1950) and references therein.

(3) (a) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem. (U.S.S.R.)*, **9**, 436 (1939); (b) L. F. Fieser and J. Rigaudy, THIS JOURNAL, **73**, 4660 (1951); (c) R. B. Turner, *ibid.*, **74**, 5362 (1952); (d) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956); (e) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (f) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957), and preceding papers; (g) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 3091 (1958).

(4) Since the completion of this work a report has appeared describing the preparation of 6-phenylcholesterol by the action of phenylmagnesium bromide on 6-ketocholestanol; see R. A. Sneen, *ibid.*, **80**, 3971 (1958).

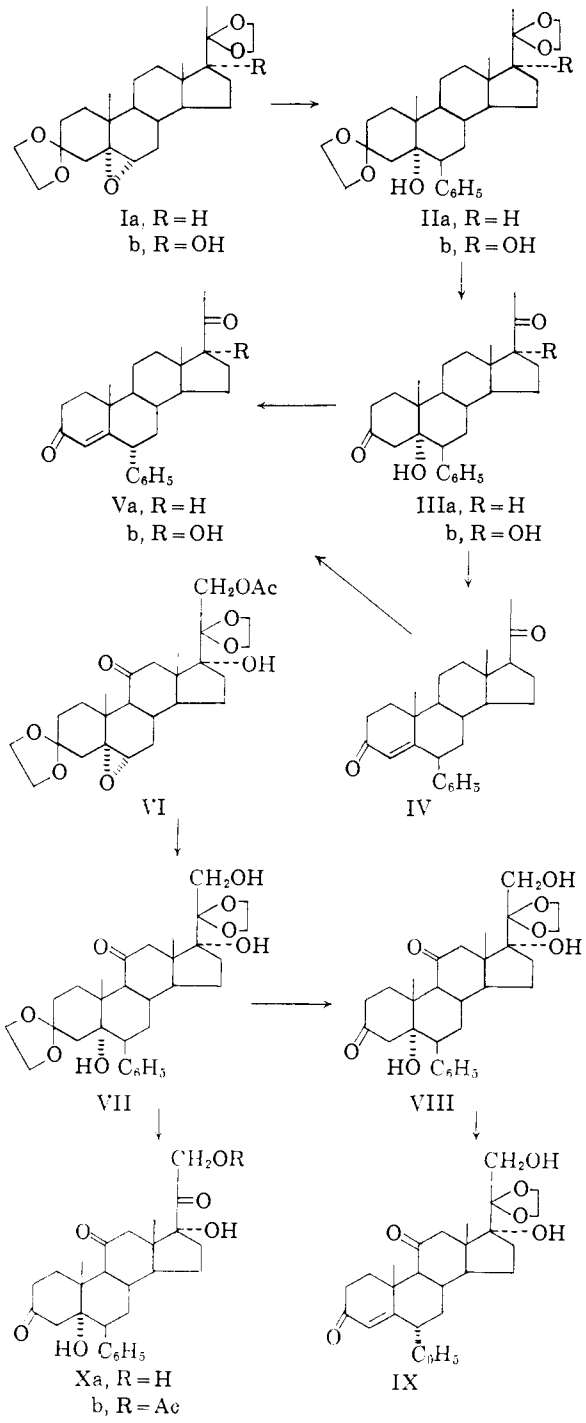
(5) The latter three bands are characteristic for monosubstituted benzenes: see L. J. Bellamy "The Infra-red Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 71, 76–77.

(6) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(7) In all cases previously observed 6α-substituted steroids have shown maxima of almost equal intensity with the parent steroid; see for example C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958), and C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *ibid.*, **80**, 4001 (1958).

(8) This substance was originally prepared in these laboratories by Dr. John Edwards and its preparation will be described in a later publication. The physical constants for 5α,6α-oxidocortisone biscycloethylene ketal acetate are m.p. 217–219°, $[\alpha]_D$ −5.4°.

(9) W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954).



ϵ 3.92, gave a positive reaction with triphenyltetrazolium chloride, indicating that the cortical side chain was still intact. It could not, however, be obtained crystalline except in small quantities and this material upon repeated recrystallization showed progressively lower extinction values in the 240 mμ region.

Alternately when the phenylhydrin bisketal VII was submitted to methanol–sulfuric acid hydrolysis[9] a non-crystalline substance was obtained which could not be purified. The material was assigned the structure Xa since it gave a positive triphenyltetrazolium chloride test and upon acetylation produced the crystalline acetate Xb albeit in very low yield. When attempts were made to dehydrate Xb to produce the Δ^4-3-ketone system the product from either acid- or base-catalyzed reactions showed spectral values similar to those obtained from IX. Again, however, the substance appeared to decompose on attempted purification as indicated by the low extinction values.

It may be pointed out that these decomposition products are not styrenes since their ultraviolet spectra are markedly different from that reported[4] for 6-phenylcholesterol.

Experimental[10]

6β-Phenyl-5α-hydroxypregnane-3,20-biscycloethylene Ketal (IIa).—A solution of 1.50 g. of 5α,6α-oxidoprogesterone-3,20-biscycloethylene ketal (Ia)[11] in 50 ml. of anhydrous tetrahydrofuran was added to 200 ml. of tetrahydrofuran containing the phenyl Grignard prepared from 3.05 g. of magnesium turnings and 20 g. of bromobenzene. After having been heated under reflux in a nitrogen atmosphere for five hours, the solution was cooled and poured into 25 ml. of cold saturated aqueous ammonium chloride. The organic phase was separated and the aqueous layer was extracted several times with ethyl acetate. After combining the organic extracts they were washed to neutrality with water, dried over sodium sulfate and evaporated to dryness leaving 1.22 g. of crystals, m.p. 187–190°. Recrystallization from ethyl acetate led to the analytical sample, m.p. 188–190°, $[\alpha]_D$ −31°, λ_{max} 254 and 260 mμ, log ϵ 2.24 and 2.31; λ_{max}^{KBr} 2.83(s), 6.27(m), 13.26(s) and 14.34(s) μ.

Anal. Calcd. for $C_{31}H_{44}O_5$: C, 74.96; H, 8.93; O, 16.10. Found: C, 75.03; H, 8.90; O, 16.22.

6β-Phenyl-5α-hydroxypregnane-3,20-dione (IIIa). (A).—One hundred mg. of bisketal IIa was dissolved in 2 ml. of acetic acid containing 5 drops of concentrated hydrochloric acid and was allowed to stand at room temperature for one hour. Dilution with 12 ml. of cold water then provided 80 mg. of crystals, m.p. 205–210°, λ_{max} 242 mμ, log ϵ 3.15. This material was adsorbed on 1.5 g. of neutral alumina whence elution with ether–benzene (1:1) yielded 60 mg., m.p. 258–260°. After three recrystallizations from acetone the pure dione IIIa was obtained, m.p. 263–265°, $[\alpha]_D$ +23°, λ_{max} 254 and 260 mμ, log ϵ 2.34 and 2.38; λ_{max}^{KBr} 2.96-(ms), 5.87(s), 6.27(w), 13.42(m) and 14.30(ms) μ.

Anal. Calcd. for $C_{27}H_{36}O_3$ $^1/_4C_3H_6O$: C, 78.77; H, 8.88. Found: C, 78.50; H, 8.90.

(B).—To 1.4 ml. of tetrahydrofuran containing 1.2 ml. of 3 *N* perchloric acid was added 100 mg. of bisketal IIa. After remaining at room temperature for 3 hours the solution was diluted with 10 ml. of cold water and the resultant crystals were collected, 80 mg., m.p. 255–258°. One recrystallization from acetone provided material identical in all respects to that isolated in the previous experiment.

6β-Phenylprogesterone (IV).—Seven ml. of pyridine containing 0.50 g. of IIIa was chilled to 0° and treated with 0.5 ml. of thionyl chloride for 8 min. The mixture then was diluted with 20 ml. of ice-water and extracted 4 times with 30 ml. of ethyl acetate. The combined extracts were washed first with dilute hydrochloric acid and then to neutrality with water. After drying over sodium sulfate and evaporation to dryness there remained a semi-solid which was taken up in acetone and treated with decolorizing carbon. Concentration of the resultant filtrate to a small volume led to 0.22 g. of crystals, m.p. 195–200°, which were obtained pure after several recrystallizations from acetone, m.p. 213–216°, $[\alpha]_D$ ±0°, λ_{max} 242 mμ, log ϵ 4.14; λ_{max}^{KBr} 5.86(s), 6.00(s), 6.25(m), 13.48(m) and 14.24(s) μ.

Anal. Calcd. for $C_{27}H_{34}O_2$: C, 83.03; H, 8.78; O, 8.19. Found: C, 82.91; H, 8.54; O, 8.52.

(10) All melting points are uncorrected. The rotations and ultraviolet spectra have been determined in chloroform and 95% ethanol, respectively, unless otherwise stated. All ketals were recrystallized in the presence of a few drops of pyridine. We would like to express our appreciation to Dr. Lewis Throop and staff for carrying out the rotational and spectral measurements.

(11) A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, 7, in press (1959).

6α-Phenylprogesterone (Va). (A) From 6β-Phenyl-5α-hydroxypregnane-3,20-dione (IIIa).—The diketone IIIa (200 mg.) was kept at room temperature overnight in 6 ml. of 1% methanolic potassium hydroxide. The solution was then diluted with 25 ml. of water and extracted 5 times with 20-ml. portions of ethyl acetate. The combined extracts were washed to neutrality with water, dried over sodium sulfate and evaporated to a small volume. In this manner there was obtained 150 mg. of crystals, m.p. 246–250°, which were obtained pure by repeated recrystallization from acetone followed by sublimation at 275° (0.001 mm.), m.p. 293–296°, $[\alpha]_D$ +69°, λ_{max} 244–246 mμ, log ε 4.11; λ_{max}^{KBr} 2.87(m), 5.90(s), 6.05(s), 6.28(w), 13.17(m) and 14.35(s) μ.

Anal. Calcd. for $C_{27}H_{34}O_2 \cdot H_2O$: C, 79.37; H, 8.88. Found: C, 79.31; H, 9.05.

(B) From 6β-Phenylprogesterone (IV).—6β-Phenylprogesterone (IV) (300 mg.) was treated under the same conditions reported under A. By these means there was obtained 200 mg. of crystals, m.p. 255–260°, which were repeatedly recrystallized from methylene chloride–hexane to provide crystals of m.p. 290–293°, $[\alpha]_D$ +72°, λ_{max} 244 mμ, log ε 4.17, and whose infrared spectrum was identical in all details to that obtained for the product in A.

6β-Phenyl-5α,17α-dihydroxypregnane-3,20-biscycloethylene Ketal (IIb).—A solution of phenylmagnesium bromide was prepared in 150 ml. of anhydrous tetrahydrofuran from 2.03 g. of magnesium and 13.3 g. of bromobenzene and to it was added 1.0 g. of the epoxide Ib.[12] By following the conditions previously described 0.60 g. of crystals was obtained, m.p. 234–236°. Two recrystallizations from ethyl acetate gave analytically pure material, m.p. 241–243°, $[\alpha]_D$ −54°; λ_{max} 254, 260 and 266 mμ, log ε 2.26, 2.32 and 2.17; λ_{max}^{KBr} 2.95(ms), 6.27(w), 13.38(ms) and 14.25(ms) μ.

Anal. Calcd. for $C_{31}H_{44}O_6$: C, 72.62; H, 8.65; O, 18.73. Found: C, 72.12; H, 8.79; O, 18.78.

6β-Phenyl-5α,17α-dihydroxypregnane-3,20-dione (IIIb).—Tetrahydrofuran (2.8 ml.) containing 0.20 g. of IIb and 2.2 ml. of 3 *N* perchloric acid was allowed to stand for 3 hours at room temperature. Dilution with water and filtration yielded 0.15 g., m.p. 258–260°, which was purified by recrystallization from ethyl acetate–methanol, m.p. 261–264°, $[\alpha]_D$ ±0° (pyridine); λ_{max} 254, 260 and 266 mμ, log ε 2.31, 2.38 and 2.29; λ_{max}^{KBr} 2.94(ms), 5.91(s), 6.28(w), 13.46(m) and 14.25(m) μ.

Anal. Calcd. for $C_{27}H_{36}O_4 \cdot {}^1/_4C_4H_8O_2$: C, 75.30; H, 8.56. Found: C, 75.31; H, 8.46.

6α-Phenyl-17α-hydroxyprogesterone (Vb).—To 4.5 ml. of 1% methanolic potassium hydroxide was added 0.15 g. of IIIb. After being kept at room temperature for 16 hours dilution with water (15 ml.) provided 0.11 g., m.p. 121–124°, λ_{max} 242 mμ, log ε 3.92. Following three recrystallizations from acetone–hexane the substance exhibited m.p. 258–261° and the value was essentially unchanged after three further recrystallizations from the same solvent pair; m.p. 259–261°, $[\alpha]_D$ −16°, λ_{max} 244–246 mμ, log ε 4.18; λ_{max}^{KBr} 2.88(ms), 5.83(s), 5.97(s), 6.22(w), 13.09(m) and 14.27(s) μ.

Anal. Calcd. for $C_{27}H_{34}O_3 \cdot H_2O$: C, 76.38; H, 8.55; O, 15.07. Found: C, 76.05; H, 8.33; O, 15.13.

(12) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barns and W. E. Dulin, THIS JOURNAL, **80**, 2904 (1958).

6β-Phenylpregnane-5α,17α,21-triol-3,11,20-trione 3,20-Biscycloethylene Ketal (VII).—Following the procedures previously described for the Grignard reaction 1.50 g. of 5α,6α-oxidocortisone biscycloethylene ketal acetate[8] provided 1.10 g. of crystals, m.p. 224–226°. A single recrystallization of this substance from ethyl acetate–methanol furnished the pure phenylhydrin VII, m.p. 225–227°, $[\alpha]_D$ ±0°; λ_{max}^{EtOH} 254, 260 and 266 mμ, log ε 2.28, 2.34 and 2.22; λ_{max}^{KBr} 2.87(s), 5.92(s), 6.27(w), 13.30(m) and 14.25(m) μ.

Anal. Calcd. for $C_{31}H_{42}O_8 \cdot C_4H_8O_2$: C, 66.64; H, 7.99; O, 25.37. Found: C, 66.95; H, 7.57; O, 25.45.

6β-Phenylpregnane-5α,17α,21-triol-3,11,20-trione 20-Ethylene Ketal (VIII).—The hydrolysis of 1.00 g. of VII by the tetrahydrofuran–perchloric acid method described above led to 0.62 g. of crystals, m.p. 265–268°. After several recrystallizations from dilute aqueous methanol the analytical sample exhibited m.p. 276–279°, $[\alpha]_D$ ±0°, λ_{max} 254 and 260 mμ, log ε 2.28 and 2.33; λ_{max}^{KBr} 2.94(s), 5.90(s), 6.26(w), 13.32(s) and 14.30(s) μ.

Anal. Calcd. for $C_{29}H_{38}O_7$: C, 69.85; H, 7.68; O, 22.46. Found: C, 69.86; H, 7.91; O, 22.44.

6α-Phenyl-Δ⁴-pregnene-17α,21-diol-3,11,20-trione 20-Ethylene Ketal (IX).—A solution containing 0.25 g. of VIII and 1.4 ml. of 0.1 *N* sodium hydroxide in 28 ml. of methanol was allowed to stand under nitrogen for 18 hours. Upon dilution with water 200 mg. of crystals was obtained, m.p. 236–238°. Repeated recrystallization from acetone led to the pure sample, m.p. 261–263°, $[\alpha]_D$ +21°, λ_{max} 236–238 mμ, log ε 4.19; λ_{max}^{KBr} 2.89(m), 5.87(s), 5.97(s), 6.24(w), 13.36(mw), 14.29(mw) μ.

Anal. Calcd. for $C_{29}H_{36}O_6$: C, 72.47; H, 7.55; O, 19.98. Found: C, 72.28; H, 7.72; O, 19.68.

6β-Phenylpregnane-5α,17α,21-triol-3,11,20-trione 21-Acetate (Xb).—To 40 ml. of methanol containing 3.8 ml. of 8% aqueous sulfuric acid was added 0.80 g. of VII. The resulting solution was heated at reflux temperature for 50 min., then diluted with ice-water. By filtration there was obtained 0.50 g. of crystals, m.p. 165–170°, no high selective ultraviolet absorption, which could not be recrystallized. After being heated on the steam-bath for 0.5 hours with 2 ml. of pyridine and 0.6 ml. of acetic anhydride, dilution with water provided 0.48 g. of crystals, m.p. 193–196°. This material was recrystallized twice from acetone and three times from methanol to obtain less than 15 mg. of the analytical sample, m.p. 250–252°, no high selective ultraviolet absorption; λ_{max}^{KBr} 2.90(ms), 5.71(s), 5.90(s), 13.25(mw) and 14.20(mw) μ.

Anal. Calcd. for $C_{29}H_{36}O_7$: C, 70.14; H, 7.31; O. 22.55. Found: C, 70.23; H, 7.39; O, 22.19.

Rotatory Dispersion Results.—The determinations were carried out by earlier described procedures[13] and were measured in dioxane solution: **6β-phenylprogesterone** (IV), *c* 0.04: $[\alpha]_{700}$ +41°, $[\alpha]_{589}$ +55°, $[\alpha]_{375}$ +171° "max," $[\alpha]_{367}$ +104° "min," $[\alpha]_{360}$ +143° "max," $[\alpha]_{350}$ +69° "min," $[\alpha]_{315}$ +1260° "max," $[\alpha]_{300}$ +206°.

6α-Phenylprogesterone (Va), *c* 0.04: $[\alpha]_{700}$ +90°, $[\alpha]_{589}$ +78°, $[\alpha]_{377}$ +505° "max," $[\alpha]_{367}$ +461° "min," $[\alpha]_{360}$ +517° "max," $[\alpha]_{355}$ +432° "min," $[\alpha]_{307}$ +1540° "max," $[\alpha]_{300}$ +860°.

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(13) See C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6377 (1956); C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).