acetamido-1,2-dideoxy-1-nitro-D-mannitol, m.p. 172–173° and $[\alpha]^{25}D$ −16.8° in water (*c* 2.4). O'Neill[5] reports m.p. 172–173° and $[\alpha]^{24}D$ −13.2° in water (*c* 1.1) for this compound.

The mother liquors from the initial reaction mixture were concentrated to a semi-crystalline mass and extracted several times by trituration at room temperature with chloroform to remove acetamide. The resulting residue was combined with the above recrystallization mother liquors, concentrated and recrystallized from ethanol to yield 2.7 g. of mixed acetamidonitroalcohols, m.p. 158–165°. Fractional recrystallization of the latter from absolute ethanol yielded a further 0.75 g. of 2-acetamido-1,2-dideoxy-1-nitro-D-mannitol (total yield, 57.5%), m.p. 172–173°, and 1.1 g. (10.4%) of 2-acetamido-1,2-dideoxy-1-nitro-D-glucitol, m.p. 155–156° and $[\alpha]^{25}D$ −12.7° in water (*c* 3.6).

Anal. Calcd. for $C_8H_{16}O_7N_2$: C, 38.1; H, 6.39; N, 11.1. Found: C, 38.1; H, 6.68; N, 10.7.

D-Mannosamine Hydrochloride and D-Glucosamine Hydrochloride.—A solution of 9.5 g. of 2-acetamido-1,2-dideoxy-1-nitro-D-mannitol in 23 ml. of 2 *N* sodium hydroxide was added dropwise to 19.5 ml. of concentrated hydrochloric acid with vigorous stirring. After the addition, the solution was brought briefly to the boiling point, again cooled to room temperature and saturated with hydrogen chloride gas. The precipitated sodium chloride was removed by filtration (Whatman no. 42 paper) and the filtrate, after dilution with an equal volume of water, was decolorized by filtration through a layer of Celite and decolorizing carbon. The solution was concentrated at reduced pressure and residual hydrogen chloride was removed from ther esulting sirup *in vacuo* over potassium hydroxide. The sirup was dissolved in 15–20 ml. of methanol containing a few drops of water and brought to crystallization by the gradual addition of acetone. Seeding crystals of D-mannosamine hydrochloride are advantageous in this initial crystallization. There was obtained 7.6 g. (93%) of nearly pure D-mannosamine hydrochloride, $[\alpha]^{25}D$ −2.9° in water (*c* 11). A single recrystallization from moist ethanol with the addition of acetone gave material with $[\alpha]^{25}D$ −3.2° in water (*c* 10). The reported[9] value in water is −3°. The product gave an X-ray powder diffraction pattern identical with that of D-mannosamine hydrochloride prepared by the alkaline isomerization of *N*-acetyl-D-glucosamine.[4,10]

2-Acetamido-1,2-dideoxy-1-nitro-D-glucitol was converted to D-glucosamine hydrochloride by the process just described except that the acidic solution from the Nef reaction was refluxed for 4 hours to complete the hydrolysis of the *N*-acetyl function. Crystallized from a small amount of water by the addition of ethanol, the product (85% yield) showed $[\alpha]^{25}D$ +68° equil. in water (*c* 1.7). A single recrystallization from water–ethanol raised this to the reported[9] value of +72°. The product gave an X-ray powder diffraction pattern identical with that of a commercial sample of D-glucosamine hydrochloride (Eastman Organic Chemicals, Rochester, N. Y.).

Acknowledgment.—The authors are pleased to acknowledge the generous support of the Corn Industries Research Foundation, Washington, D.C., during the course of this work.

(9) R. Kuhn, W. Bister and H. Fischer, *Ann.*, **617**, 109 (1958).

(10) We are indebted to Dr. Saul Roseman, Rackham Arthritis Research Unit, University of Michigan, for this latter sample and to Mr. A. V. Guzzo of this Laboratory for the X-ray diffraction measurements.

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

Steroids. CXXXI.[1] A New Series of 6-Substituted Progesterone Analogs

BY JOHN A. ZDERIC AND DINORAH CHAVEZ LIMON

RECEIVED JUNE 18, 1959

Treatment of 5α,6α-oxidoprogesterone bis-ethyleneketal with acetylene dimagnesium bromide led to 6β-ethynylpregnane-5α-ol-3,20-dione bis-ethyleneketal which, following hydrolysis of the ketal functions and dehydration of the 5α-hydroxyl group, provided 6β-ethynylprogesterone. While this substance could not be inverted to the corresponding 6α-ethynyl epimer, it was capable of conversion to 6α-(1-chlorovinyl)-progesterone and 6α-acetyl-progesterone. By controlled reductions of the original ethynylated fission product either 6β-vinyl or 6β-ethylpregnane-5α-ol-3,20-dione bis-ethyleneketal could be obtained. These compounds were then converted by appropriate manipulation to 6α-ethylprogesterone and 6β-vinylprogesterone.

Our recent observation[2] that steroid 5α,6α-epoxides upon treatment with phenylmagnesium bromide may be readily opened to provide 6-phenylated steroids, prompted us to undertake a similar investigation of epoxide openings employing acetylene dimagnesium bromide. While *a priori* it was conceivable that the use of this reagent could lead to a bis-substituted ethyne the possibility appeared remote since it had already been observed[3] that steroidal 17-ketones upon treatment with acetylene dimagnesium bromide provided exclusively the monosubstituted ethyne. On the basis of this earlier work as well as the present instance where only a monosubstituted ethyne was formed, it appears that the steric environment of the reactive center is the controlling factor governing mono- or disubstitution.[4]

Thus when 5α,6α-oxidopregnene-3,20-dione bis-ethyleneketal[5] was treated with acetylene dimagnesium bromide in tetrahydrofuran at reflux temperature the epoxide generally was smoothly opened to provide 6β-ethynylpregnane-5α-ol-3,20-dione bis-ethyleneketal (IIa) in 85% yield. Unexplicably on occasion the yields were less than 10% and in these cases the residues were non-crystalline and on the basis of infrared spectroscopy appeared to be free of either mono- or disubstituted ethynes.[6] No attempt was made to characterize this material.

Upon treatment of IIa with aqueous perchloric acid in tetrahydrofuran[7] the ketal functions were hydrolyzed in high yield to provide the corresponding dione IIIa. Dehydration of IIIa with thionyl chloride in pyridine then led to 6β-ethynylprogesterone (IVa); fully characterized by elemental

(1) Paper CXXX, J. A. Zderic, H. Carpio and C. Djerassi, THIS JOURNAL, **82**, 446 (1960).

(2) J. A. Zderic and D. Chávez Limón, *ibid.*, **81**, 4570 (1959).

(3) F. Sondheimer, O. Mancera, H. Flores and G. Rosenkranz, *ibid.*, **78**, 1742 (1956).

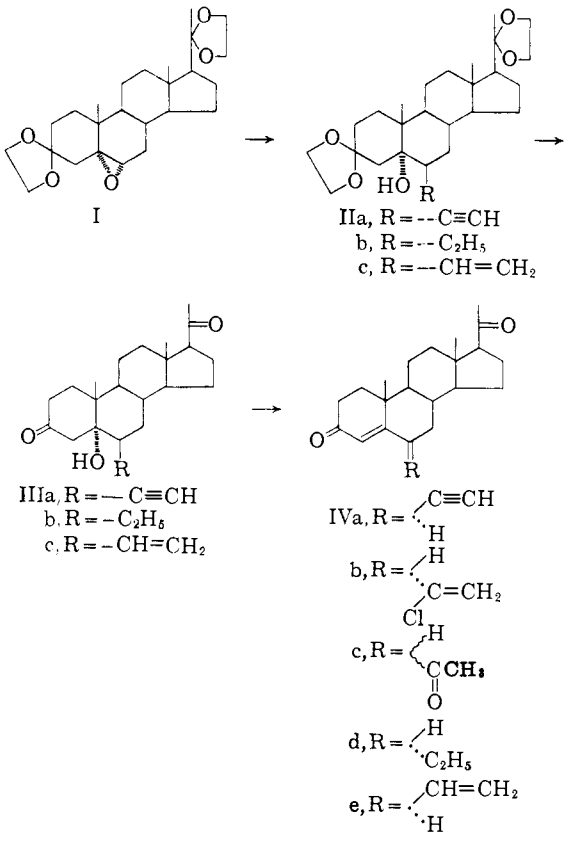
(4) For an example of disubstitution see, O. Isler, H. Lindlar, M. Montavon, R. Rüegg and P. Zeller, *Helv. Chim. Acta*, **39**, 249 (1956).

(5) A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

(6) For a description of the bands associated with ethynes see L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 57–62.

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

analysis, spectral data and its rotatory dispersion curve which was characteristic for a 6β-substituted progesterone.[8] When alkaline inversion (room temperature overnight with dilute methanolic potassium hydroxide) of IVa was attempted in order to obtain the 6α-equatorial ethynyl derivative, the resultant product was non-crystalline and exhibited λ_{max}^{EtOH} 242 mμ, log ϵ 3.90. The infrared spectrum of this substance no longer exhibited the strong C–H stretch band at 3.07 μ and repeated attempts at crystallization were unsuccessful even after careful chromatography. In contrast



to this result, when IVa was observed spectroscopically following the addition of one drop of 0.1 *N* methanolic potassium hydroxide, the ultraviolet spectrum rapidly shifted from the normal reading of λ_{max}^{EtOH} 236–238 mμ, log ϵ 4.17, to λ_{max}^{EtOH} 237–242 and 280 mμ, log ϵ 4.13 and 4.31. Such a change perhaps finds some analogy in the recent work of Bowers, *et al.*,[9] who upon observing a similar spectrum for the dehydration product of 6β-cyanopregnane-5α-ol-3,20-dione postulated their substance to be a mixture of 6α-cyanoprogesterone and the corresponding enol 6-cyano-$\Delta^{3,5}$-pregnadiene-3-ol-20-one. Whether such a system is actually present in the case at hand is not clear since the intensity of the 240 mμ maximum may be attributable to a mixture of Δ^4-3-ketone and enolate or possibly solely to the enolate. That it is possible for an enolate of this type to absorb strongly in the 240 mμ region follows from the observation made on the enolate of 6ξ-acetylprogesterone, *vide infra*.

While in the present work this point was not pursued further, it appears likely that the double maxima substance observed spectroscopically must be an intermediate in the formation of the product with a single maximum obtained by overnight alkaline treatment.

We next turned our attention to the possibility of an acid-catalyzed inversion. When IVa was treated at room temperature with a few drops of concentrated hydrochloric acid in acetic acid inversion did occur but only with concomitant addition of hydrogen chloride across the triple bond to provide in high yield 6α-(1-chlorovinyl)-progesterone (IVb). The structure of this compound was apparent not only from its analytical data but also from the infrared spectrum which exhibited the very characteristic terminal methylene band at 11.22 μ and its rotatory dispersion curve which was of the 6α-substituted progesterone type.[8] The addition of hydrogen chloride across the triple bond in this case is curious since 17α-ethynylated steroids are in general not affected under these reaction conditions.[10]

In the hope that inversion might still be effected under acidic conditions, the reaction of 6β-ethynylprogesterone (IVa) in acetic acid containing a few drops of sulfuric acid was investigated next. From this medium there was obtained in very low yield a single pure crystalline substance which exhibited λ_{max}^{KBr} 5.88 5.92 and 6.02 μ. While this material possessed an ultraviolet spectrum, λ_{max}^{EtOH} 246 mμ, log ϵ 4.12, characteristic for certain 6-substituted Δ^4-3-ketones,[11] the spectrum was rapidly shifted by the addition of one drop of 0.1 *N* alkali to λ_{max}^{EtOH} 240 mμ and 420 mμ, log ϵ 4.05 and 4.00.[12] Upon acidification with acetic acid, the spectrum again shifted to exhibit λ_{max}^{EtOH} 240 mμ and 320 mμ, log ϵ 4.10 and 4.04.[13] This spectral behavior combined with the elemental analysis led to the assignment of 6ξ-acetylprogesterone (IVc) as

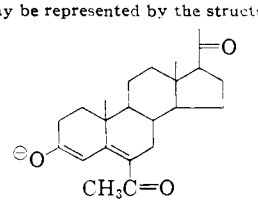
(8) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1958), have shown that 6β-methyl-Δ^4-3-keto steroids exhibit dispersion curves where the characteristic multiple Cotton effect between 350–380 mμ occurs at a rather high rotation and that this then drops as one proceeds to lower wave lengths. This is not true of 6α-equatorially substituted Δ^4-3-ketones where the rotation rises progressively below 350 mμ. The rotatory dispersion curve of progesterone (E. W. Foltz, A. E. Lippman and C. Djerassi, *ibid.*, **77**, 4359 (1955)) represents roughly the summation of the individual contributions of the Δ^4-3-ketone and the 20-keto group. Consequently 6α-substituted progesterones exhibit rotatory dispersion curves which are very similar to that of progesterone itself. On the other hand, 6β-substituted ones in general show a rotatory elevation of the multiple Cotton effect between 350–380 mμ and an appreciable lowering of the peak near 315 mμ due to the 20-keto group.

(9) A. Bowers, E. Denot, M. B. Sánchez, L. M. Sánchez-Hidalgo and H. J. Ringold, *ibid.*, **81**, 5233 (1959).

(10) Unpublished observations from these laboratories both in the 10-methyl and 19-nor series.

(11) For example, 6β-bromo-Δ^4-3-ketones absorb in this region; C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1950).

(12) This enol may be represented by the structure



(13) The alkaline and acidified spectra were measured on less than 0.25 mg. of sample diluted in 10 ml. of ethanol and therefore can only be considered as qualitative in nature.

the structure of the reaction product. Insufficient material was available to determine the rotatory dispersion curve and thus the configuration at C-6.

For the preparation of 6α-ethylprogesterone (IVd) the catalytic reduction of IIa was effected with 5% palladium–carbon catalyst to provide 6β-ethylpregnane-5α-ol-3,20-dione bis-ethyleneketal (IIb). Surprisingly this compound could not be hydrolyzed to the corresponding ketal-free 6β-ethyl-5α-ol-3,20-dione IIIb without extensive dehydration of the 5α-hydroxyl group. While IIIb was obtainable in low yield by the catalytic reduction of 6β-ethynylpregnane-5α-ol-3,20-dione (IIIa), it proved convenient to submit directly the total crude perchloric acid hydrolysis product of IIb to the action of thionyl chloride in pyridine. By this sequence 6α-ethylprogesterone (IVd) resulted, the configuration being determined on the basis of the rotatory dispersion curve.[8] Proof that the assignment of configuration was correct was provided by the fact that IVd could be recovered unchanged after overnight treatment with alkali, conditions which ordinarily invert 6β-*axial* substituents to their more stable 6α-*equatorial* forms. That the product isolated here was of the 6α- rather than the expected 6β-donfiguration which results from thionyl chloride–pyridine dehydrations [14] may find some explanation in increased *non-bonded interactions* between the 10β-methyl and 6β-axial ethyl groups. It is interesting to note that no such problem was encountered in the isolation of 6β-phenylprogesterone[2] and this is perhaps a reflection of the very large difference in effective bulk between the planar phenyl ring and the ethyl group. Indeed it may be that not only the facile inversion but also the partial dehydration of the 5α-hydroxyl group in IIIb are promoted by the release of this steric compression.

When 6β-ethynylpregnane-5α-ol-3 20-dione bis-ethyleneketal (IIa) was allowed to absorb one mole of hydrogen using 3% palladium–calcium carbonate catalyst in pyridine, the corresponding 6β-vinyl compound IIc was produced in fair yield as one of two possible polymorphic modifications. Alternatively this same reduction could be accomplished by the action of sodium metal in liquid ammonia.[15] Upon ketal hydrolysis 6β-vinylpregnane-5α-ol-3 20-dione (IIIc) was obtained and this was readily dehydrated to provide 6β-vinylprogesterone (IVe). Similar to the 6β-ethynyl case it was not possible to effect an alkaline inversion of IVe to the corresponding 6α-vinyl derivative only gums being obtained which possessed a single maximum in the 242 mμ region.

Upon treatment of 6β-vinylprogesterone (IVe) with acetic acid containing a few drops of concentrated sulfuric acid a new and unidentified product was obtained in 80% yield. This substance, m.p. 136–138°, gave analytical values which accorded for an isomer of IVe and was characterized by a very high positive rotation, $[\alpha]_D$ +435°, as well as a double maxima in the ultraviolet, λ_{max}^{EtOH} 244 and 280 mμ, log ε 3.95 and 4.04, which was not affected by the addition of a drop of 0.1 *N* alkali. The infrared spectrum possessed strong bands at 5.87 and 5.99 μ and a medium strong band at 6.24 μ but did not show any band corresponding to a terminal methylene.

On the basis of these data one cannot completely discount the possibility that the 6β-vinylprogesterone (IVe) was contaminated with a rather large amount (based on the ε-value at 244 mμ) of 6α ethylprogesterone (IVd), arising from overreduction in the conversion IIa to IIc. Such a condition would, of course, provide an explanation for the maxima at 244 (6α-ethylprogesterone) and 280 mμ (6-ethylideneprogesterone, resulting from double bond isomerization). The evidence against such a conclusion rests on two points. First, there are the facts that both the new product, m.p. 136–138°, and the 6β-vinylprogesterone (IVe) used in its preparation were completely homogeneous by paper chromatography while employing several different solvent systems. Second, there is the observation that the rotatory dispersion curve of IVe appears normal for a 6β-substituted progesterone, R.D. $[\alpha]_{307}$ +2190°, as compared to 6β-ethynylprogesterone (IVa), R.D. $[\alpha]_{312}$ +2030°, or 6β-methylprogesterone,[14] R.D. $[\alpha]_{307}$ +2375°. Had IVe contained any considerable amount of 6α-ethylprogesterone (IVd), R.D. $[\alpha]_{305}$ +3770°, one could reasonably have expected an intensified maximum instead of the observed value of +2190°. Likewise the possibility of contamination with 6β-ethylprogesterone may be readily discounted due to the inherent configurational instability of this compound (*vide supra*). In any case, for the present time the exact nature of this reaction product remains unknown.

The biological activities, as progestational agents, of IVb and IVc were measured in the standard Clauberg assay whereas IVa, IVd and IVe were measured in the guinea pig copulatory assay.[16] In both assays the subcutaneous route was employed. At dose levels where progesterone gave a maximal response, 6α-(1-chlorovinyl)-progesterone (IVb), 6ξ-acetylprogesterone (IVc) and 6β-vinylprogesterone (IVe) were found to be essentially inactive while 6β-ethynylprogesterone (IVa) was about 25% as active as progesterone. In preliminary assays 6α-ethylprogesterone (IVd) exhibited an activity equal to that of progesterone.

Acknowledgment.—The authors are indebted to Drs. H. J. Ringold and C. Djerassi for aid in the preparation of this manuscript.

Experimental[17]

6β-Ethynylpregnane-5α-ol-3,20-dione bis-ethyleneketal (IIa).—A steady stream of acetylene gas was allowed to bubble through a solution of 100 ml. of anhydrous tetrahydrofuran and 25 ml. of methylmagnesium bromide for 3 hours. After this time the acetylene stream was interrupted and 1.0 g. of 5α,6α-oxidoprogesterone bis-ethyleneketal (I)[5] in 50 ml. of anhydrous tetrahydrofuran was added all at once. The resulting mixture was then heated at reflux temperature for 20 hours whereafter it was decomposed over cold saturated aqueous ammonium chloride. Following

(14) See for example ref. 2 and H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(15) K. N. Campbell and L. T. Eby, THIS JOURNAL, **63**, 216 (1941).

(16) All bioassays were conducted by the Endocrine Laboratories, Madison, Wis.

(17) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet spectra in 95% ethanol unless otherwise specified. We are indebted to Dr. L. Throop and staff for the rotation and spectral measurements.

ethyl acetate extraction, the extracts were washed with water, dried over sodium sulfate and evaporated to leave 1.0 g. of non-crystalline material. This substance was then passed through 30 g. of alumina in hexane whence from the early fractions there was obtained 0.79 g., m.p. 136–140°, which after one recrystallization from acetone provided the analytical sample, m.p. 144–146°, $[\alpha]_D$ −37°; λ_{max}^{KBr} 2.90 (ms), 3.07(ms)μ.

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07; O, 17.99. Found: C, 72.75; H, 8.79; O, 18.03.

6β-Ethylnylpregnane-5α-ol-3,20-dione (IIIa).—To 5.2 ml. of tetrahydrofuran containing 0.26 g. of IIa was added 4.1 ml. of 3 *N* aqueous perchloric acid and the resulting solution was kept at room temperature for 3 hours. Following dilution with 5 ml. of ice-water and filtration there was obtained 0.20 g., m.p. 270–275°, which was purified by several recrystallizations from methanol, m.p. 282–285° dec., $[\alpha]_D$ +51°; λ_{max}^{KBr} 3.00(ms), 5.84(s), 5.93(s)μ.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05; O, 13.46. Found: C, 78.02; H, 9.19; O, 13.15.

6β-Ethynylprogesterone (IVa).—Thionyl chloride (0.5 ml.) was added to a solution of pyridine (5 ml.) and 0.30 g. of IIIa. After being kept at 0° for 3 min. the mixture was diluted with water and the resultant 0.22 g. of semi-solid crystals was collected. Three recrystallizations from methanol led to the analytical sample, m.p. 180–184°, $[\alpha]_D$ +46° (dioxane), λ_{max} 236–238 mμ, log ϵ 4.17; λ_{max}^{KBr} 3.13-(s), 5.91(vs), 6.00(vs), 6.22(w)μ; R.D. in dioxane (*c* 0.065): $[\alpha]_{700}$ +29°, $[\alpha]_{589}$ +46°, $[\alpha]_{377}$ +485°, $[\alpha]_{370}$ +465°, $[\alpha]_{365}$ +546°, $[\alpha]_{350}$ +494°, $[\alpha]_{312}$ +2030°, $[\alpha]_{300}$ +1286°.

Anal. Calcd. for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93; O, 9.46. Found: C, 81.75; H, 9.15; O, 8.69.

6α-(1-Chlorovinyl)-progesterone (IVb).—To 2 ml. of acetic acid containing 0.10 g. of 6β-ethynylprogesterone (IVa) was added 4 drops of concentrated hydrochloric acid. After 1.75 hours at room temperature water was added and the mixture was extracted with ethyl acetate. The extract was then washed twice with water, dried over sodium sulfate and evaporated to leave a residue which was passed through 3 g. of neutral alumina. From the first two fractions there was obtained *ca.* 60 mg., m.p. 145–160°, which was obtained pure after several recrystallizations from ether, m.p. 158–161°, $[\alpha]_D$ +94° (dioxane), λ_{max}^{EtOH} 240 mμ, log ϵ 4.16 λ_{max}^{KBr} 5.88(s), 5.99(vs), 6.14(m), 6.24(m), 11.22(s)μ; R.D. in dioxane (*c* 0.054): $[\alpha]_{700}$ +71°, $[\alpha]_{589}$ +94°, $[\alpha]_{310}$ +4120°, $[\alpha]_{300}$ +2210°.

Anal. Calcd. for $C_{23}H_{31}O_2Cl$: C, 73.68; H, 8.33; O, 8.54. Found: C, 73.62; 73.83; H, 8.26, 8.33; O, 8.59.

6ξ-Acetylprogesterone (IVc).—Three ml. of acetic acid containing 0.30 g. of IVa and 3 drops of concentrated sulfuric acid was allowed to stand for 40 min. at room temperature. The resultant deep green fluorescent solution was then diluted with water, extracted with ethyl acetate and the extracts were washed with water, dried and evaporated. The residue was crystallized from ether to provide 50 mg., m.p. 173–176°, which after one further crystallization from acetone provided a sample whose m.p. was unchanged upon repeated recrystallization, m.p. 190–191°, λ_{max} 246 mμ, log ϵ 4.12, containing 1 drop of aqueous 0.1 *N* sodium hydroxide λ_{max}^{EtOH} 240 and 420 mμ, log ϵ 4.05 and 4.00[13]; λ_{max}^{KBr} 5.88(s), 5.92(s), 6.02(s), 6.28(m)μ; $[\alpha]_D$ −199°.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 76.92; H, 8.82.

6β-Ethylpregnane-5α-ol-3,20-dione bis-ethyleneketal (IIb).—To 70 ml. of methanol containing 80 mg. of pre-reduced 5% palladium-on-carbon was added 0.30 g. of IIa. After 0.5 hour two equivalents of hydrogen had been consumed and the mixture was filtered and evaporated. The residue was then passsed in hexane through 10 g. of alumina and the initial fractions were combined and recrystallized from pentane to provide 0.15 g., m.p. 155–158°. Upon further recrystallization from acetone the pure sample was obtained, m.p. 160–162°.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89; O, 17.83. Found: C, 72.55; H, 9.56; O, 18.18.

6β-Ethylpregnane-5α-ol-3,20-dione (IIIb).—A 1.0-g. sample of IIIa was added to 35 ml. of methanol containing 0.10 g. of pre-reduced 5% palladium-on-charcoal. The hydrogenation was allowed to proceed overnight after which time the catalyst was filtered and the solvent evaporated. The residue was then treated in methanol solution with decolorizing carbon and after concentration there was obtained 0.25 g. of almost white crystals, m.p. 239–242°. From the mother liquors there was obtained an additional 0.35 g. m.p. 209–212°. Repeated recrystallizations from methanol were necessary to obtain *ca.* 15 mg. of the final sample, m.p. 257–259°.

Anal. Calcd. for $C_{23}H_{36}O_3 + {}^1/_4\ CH_4O$: C, 75.77; H, 10.12; O, 14.11. Found: C, 76.07; H, 9.75; O, 13.81.

6α-Ethylprogesterone (IVd).—To 3 ml. of tetrahydrofuran containing 150 mg. of IIb (m.p. 159–161°) was added 2.3 ml. of 3 *N* perchloric acid. After three hours at room temperature the solution was diluted with water and extracted with ethyl acetate. The extracts were then washed with water, dried and evaporated to leave a non-crystalline residue, 130 mg., λ_{max} 242 mμ, log ϵ 3.97. Without purification this product was treated for 3 min. at 0° with 0.15 ml. of thionyl chloride in 2 ml. of pyridine. After dilution with water and ethyl acetate extraction, the extracts were washed with water dried and evaporated to leave an oily residue, λ_{max} 242 mμ, log ϵ 4.07. From this material following adsorption on 3 g. of neutral alumina and hexane elution, there was obtained 75 mg. of crystals, m.p. 89–95°. Following treatment with decolorizing carbon in acetone and several recrystallizations from acetone–hexane the analytical sample was obtained, 28 mg., m.p. 166–167°, $[\alpha]_D$ +191° (dioxane), λ_{max} 242–244 mμ, log ϵ 4.22; R.D. in dioxane (*c* 0.066): $[\alpha]_{700}$ +122°, $[\alpha]_{589}$ +191°, $[\alpha]_{360}$ +1164°, $[\alpha]_{350}$ +1091°, $[\alpha]_{305}$ +3770°, $[\alpha]_{300}$ +3330°.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.93; H, 9.86.

6β-Vinylpregnane-5α-ol-3,20-dione Bis-ethyleneketal (IIc). A. By Sodium–Liquid Ammonia Reduction of IIa.—A solution of tetrahydrofuran (40 ml.) and 3.5 g. of IIa was added with vigorous stirring to 500 ml. of liquid ammonia containing 3 g. of sodium. After 2 hours the excess sodium was destroyed by the cautious addition of 5 ml. of methanol and the remaining ammonia was allowed to evaporate. The residue was then diluted with water and extracted with ethyl acetate whereafter the extracts were washed with water, dried and evaporated. The remaining material was then passed in hexane solution through 40 g. of neutral alumina and the initial fractions were triturated with cold pentane to provide 3.08 g. of crystals, m.p. 123–126°, which after further crystallization from the same solvent provided IIc with m.p. 128–130°, $[\alpha]_D$ −39°. Upon admixture with the material prepared in **B**, the mixture exhibited m.p. 125–130°.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48; O, 17.91. Found: C, 72.53; H, 9.40; O, 18.21.

B. By Catalytic Reduction of IIa.—Pyridine (45 ml.) containing 0.9 g. of pre-reduced 2% palladium-on-carbon and 0.60 g. of IIa was allowed to stir at room temperature for 26 min. in an atmosphere of hydrogen. At that time approximately one equivalent of hydrogen had been consumed and the reaction mixture was filtered and evaporated. The residue was then crystallized three times from pentane to provide 0.40 g. of pure IIc, m.p. 99–101°, $[\alpha]_D$ −38°; λ_{max}^{KBr} 2.91(m), 6.13(w), 10.92(ms)μ.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48; O, 17.91. Found: C, 73.03; H, 9.37; O, 17.80.

6β-Vinylpregnane-5α-ol-3,20-dione (IIIc).—To 5 ml. of tetrahydrofuran containing 0.35 g. of IIc was added 3.9 ml. of 3 *N* perchloric acid. After 3 hours at room temperature the solution was diluted with water and the resultant crystals were collected, 90 mg., m.p. 205–210°. Several recrystallizations from ethyl acetate led to the analytical sample, m.p. 260–263°, $[\alpha]_D$ −37°; λ_{max}^{KBr} 3.00(ms), 5.85(s), 5.93(s), 10.99(m)μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 76.77; H, 9.41; O, 13.58.

6β-Vinylprogesterone (IVe).—A 0.20-g. sample of IIIc was dissolved in 2.5 ml. of pyridine and treated for 3 min. at 0° with 0.2 ml. of thionyl chloride. Dilution with water then provided 0.10 g., m.p. 140–142°, which was recrystallized twice from ether–hexane to provide the 6β-vinyl derivative IVe, m.p. 150–152°, $[\alpha]$ +103°, λ_{max} 240–242 mμ, log ϵ 4.19; λ_{max}^{KBr} 5.87(s), 6.00(s), 6.26(w), 10.80(m)μ; R.D. in dioxane (*c* 0.061): $[\alpha]_{700}$ +62°, $[\alpha]_{589}$ +65°, $[\alpha]_{372}$ +728°, $[\alpha]_{365}$ +677°, $[\alpha]_{362}$ +747°, $[\alpha]_{360}$ +714°, $[\alpha]_{350}$ +813°, $[\alpha]_{345}$ +741°, $[\alpha]_{307}$ +2190°, $[\alpha]_{300}$ +1534°.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47; O, 9.40. Found: C, 81.00; H, 9.22; O, 9.58.

Action of Sulfuric Acid on 6β-Vinylprogesterone (IVe).— To 0.20 g. of 6β-vinylprogesterone (IVe) in 2 ml. of acetic acid was added 2 drops of concentrated sulfuric acid. After 20 min. at room temperature the solution was diluted with water and extracted with ethyl acetate. The extracts were then washed with water, dried and evaporated to leave a crystalline residue, 0.17 g., m.p. 130–133°, which was further purified by recrystallization from ether–hexane, m.p. 136–138°, $[\alpha]D$ +435°, λ_{max}^{EtOH} 244 and 278–280 mμ, log ε 3.95 and 4.04, unaltered by the addition of a drop of 0.1 *N* alkali; λ_{max}^{KBr} 5.87(s), 6.00(s) and 6.23(m)μ.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47; O, 9.40. Found: C, 81.00; H, 9.44; O, 9.91.

APARTADO POSTAL 2679, MÉXICO, D. F.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND BIOCHEMISTRY DEPARTMENTS OF SCHERING CORP.]

Halogenated Progesterones. I. 9α,11β-Dihaloprogesterones

BY HANS REIMANN, EUGENE P. OLIVETO, RUDOLPH NERI, MILTON EISLER AND PRESTON PERLMAN

RECEIVED SEPTEMBER 16, 1959

A number of 9α,11β-dihaloprogesterones and 9α,11β-dihalo-1-dehydroprogesterones have been prepared from the corresponding 9(11)-dehydro compounds by the addition of chlorine and mixed halogens. The parenteral progestational activity of these compounds, measured in rabbits, is reported.

In recent years a number of analogs of progesterone, some of which have shown interesting physiological activity, have been prepared. These have included the 6α-methyl,[1] 17α-methyl,[2] 6-fluoro,[3] 21-fluoro,[4] 17α-bromo,[5] 17α-acetoxy[6] and 11-dehydro[7] derivatives of progesterone, and various combinations thereof. Some 9α-halo-11β-hydroxy- and 11-keto-progesterones[8] have also shown progestational activity.[9] This paper describes a new class of steroids which are active in the McPhail progestin assay in rabbits, 9α,11β-dihaloprogesterones.[10]

When 9(11)-dehydroprogesterone (I)[12] was chlorinated with one mole of chlorine (gaseous or derived from N-chlorosuccinimide and hydrogen chloride) either in acetic acid containing an excess of chloride ion or in carbon tetrachloride containing several moles of pyridine[13] a dichloroprogesterone was isolated which was assigned the structure 9α,11β-dichloroprogesterone (II). Similarly, treatment of I with one mole of N-bromoacetamide in the presence of hydrogen chloride and excess chloride ion in acetic acid[11a] or with one mole of N-bromoacetamide in the presence of hydrogen fluoride in diethylacetic acid[11a] resulted in the formation, respectively, of 9α-bromo-11β-chloroprogesterone (III) and 9α-bromo-11β-fluoroprogesterone (IV). These structural assignments are based, in addition to analogy with similar additions in other series,[11,14] on the following considerations.

The ultraviolet and infrared spectra are in accord with the proposed structures, showing evidence for an intact 4-ene-3-one system. Treatment of II with chromous chloride in acetone resulted in ready transformation to I; under these conditions a 2-chloro-4-ene-3-one is essentially inert.[15] Further evidence of addition (necessarily at 9(11) in view of the spectroscopic evidence) rather than substitution (at 2,6,17 or 21) taking place lies in the isolation of the mixed dihalo compounds (if an ionic mechanism is assumed). While it is possible to ascribe the formation of the bromochloro compound III to substitution by chlorine and bromine *via* the equilibrium $2BrCl \rightleftarrows Br_2 + Cl_2$, this pathway appears to be impossible in the case of the bromofluoro compound IV in which case only $F^{\ominus}$ is available.[16] It seems reasonable to extend this result to the other compounds in the series.

The assigned stereochemistry is based on initial attack by the positive halogen from the less hindered α-side[17] followed by the attack of the negative ion to give the *trans*-diaxial addition product.[18] The ultraviolet spectra of dihaloprogesterones show the expected lower absorption

(1) (a) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (b) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

(2) H. H. Günthard, E. Beriger, C. R. Engel and H. Heusser, *Helv. Chim. Acta*, **35**, 2437 (1952), and references cited there.

(3) (a) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958); (b) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chemistry & Industry*, 1002 (1958).

(4) P. Tannhäuser, R. J. Pratt and E. V. Jensen, THIS JOURNAL, **78**, 2658 (1956).

(5) C. R. Engel and H. Jahnke, *Canad. J. Biochem. Physiol.*, **35**, 1047 (1957).

(6) R. B. Turner, THIS JOURNAL, **75**, 3489 (1953).

(7) C. Meystre, E. Tschopp and A. Wettstein, *Helv. Chim. Acta*, **31**, 1463 (1948).

(8) J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, THIS JOURNAL, **77**, 1068 (1955).

(9) J. Fried, W. B. Kessler and A. Borman, *Ann. N. Y. Acad. Sci.*, **71**, 494 (1958).

(10) 9α,11β-Dihalo-11-desoxycorticosteroids[11a,b] and 9α,11β-dihalo-1,4-androstadiene-3,17-diones[11a] have recently been described.

(11) (a) C. H. Robinson, L. Finckenor, E. P. Oliveto and D. Gould, THIS JOURNAL, **81**, 2191 (1959); (b) S. K. Figdor, Abstracts of the Meeting of the American Chemical Society, Chicago, Ill., Sept. 11, 1958, p. 66-P.

(12) (a) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943); (b) G. Rosenkranz, O. Mancera and F. Sondheimer, THIS JOURNAL, **76**, 2227 (1954).

(13) We wish to thank Dr. C. H. Robinson for suggesting this procedure.

(14) R. E. Buckles (THIS JOURNAL, **71**, 1157 (1949)) used N-bromoacetamide with hydrogen bromide to convert olefins to dibromides and later studied similar additions using N-bromoacetamide and hydrogen chloride to give bromochloro compounds (R. E. Buckles and J. W. Long, *ibid.*, **73**, 998 (1950)). J. B. Ziegler and A. C. Shabica (*ibid.*, **74**, 4891 (1952)) employed N-bromoacetamide and hydrogen chloride to convert cholesterol to 5α-bromo-6β-chlorocholestanol.

(15) J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, *ibid.*, **75**, 3500 (1953).

(16) The possibility of disubstitution by bromine, followed by replacement of one bromide by fluoride, is considered very unlikely under the reaction conditions.

(17) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(18) *Cf.* the addition of hypoiodous acid (ref. 8 and 19) and of acyl hypohalite (ref. 20 and S. G. Levine and M. E. Wall, THIS JOURNAL, **81**, 2826 (1959)) to 9(11)-dehydro steroids