STEROIDS AND RELATED PRODUCTS

XXI. THE SYNTHESIS OF 17α-BROMO-6α-METHYLPROGESTERONE[1, 2]

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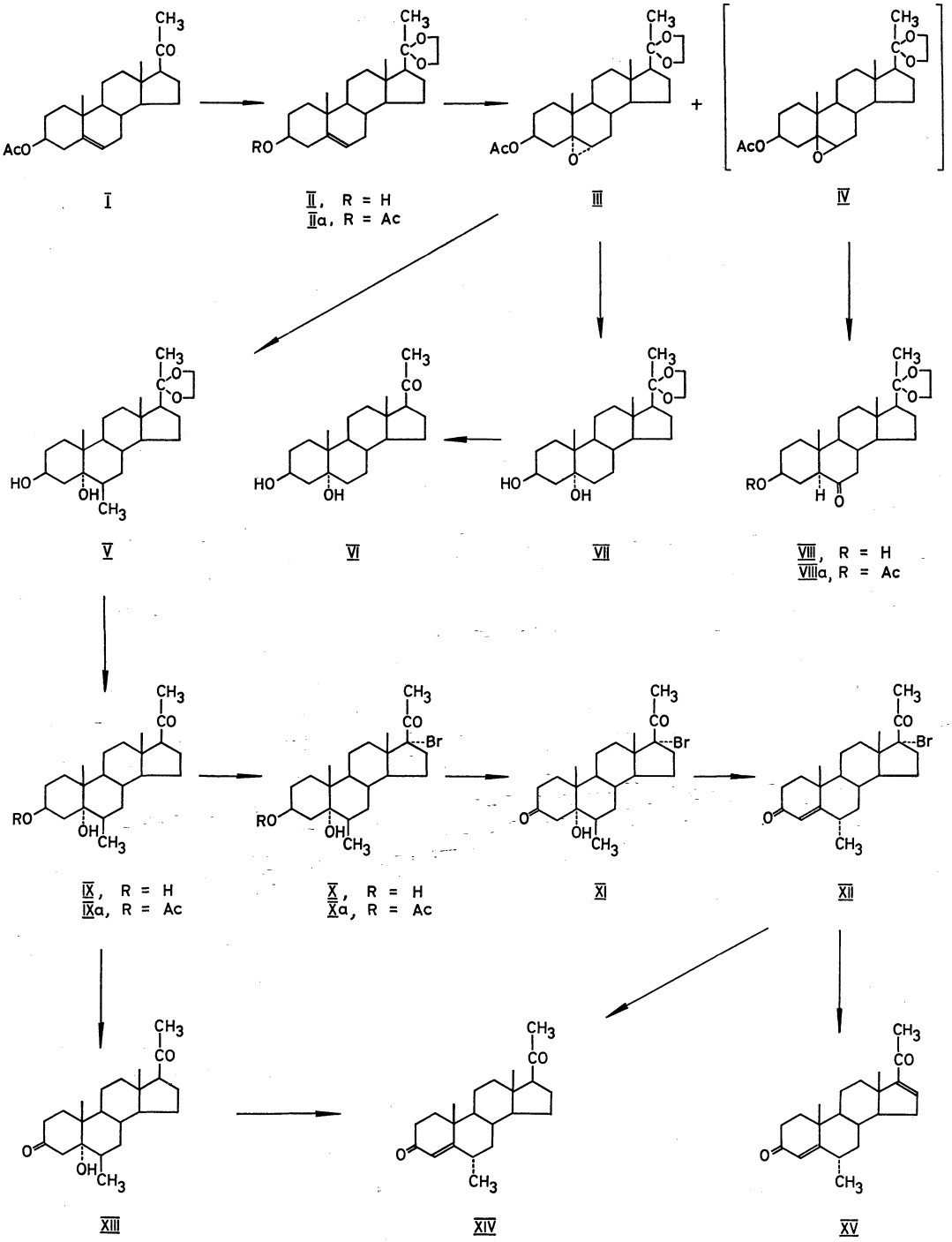
ABSTRACT

The synthesis fo 17α-bromo-6α-methylprogesterone, from pregnenolone acetate, is reported. The product is a potent luteoid with marked oral activity. In the course of this investigation, a useful variation of the synthesis of 6α-methylprogesterone, from pregnenolone, was devised. The rearrangement of a 5β,6β-epoxide to a 6-ketone, upon chromatography on aluminum oxide "Woelm", was observed.

A few years ago, this group reported the synthesis and marked progestational activity of 17α-bromoprogesterone (2). As we exposed recently (3), we considered that it would be useful to establish whether or not the enhancing effect on progestational activity of the 17α-bromine substituent is an isolated phenomenon in the case of 17α-bromoprogesterone, particularly in view of our thesis that bulky 17α-substituents increase, in general, the luteoid activity of 20-keto steroids of the progesterone type (cf. ref. 4). The investigation of 6α-substituted 17α-bromoprogesterones seemed attractive since it was known that the introduction of various 6α-substituents might lead to potentiation of the progestational activity, in particular of the oral progestational activity (cf. refs. 4–10 and 13, 14 of the article quoted as ref. 3). In a first paper (3), we reported the synthesis and considerable luteoid activity of 6α-fluoro-17α-bromoprogesterone (cf. also refs. 4 and 5[4]); in the present paper, we record the synthesis and high progestational activity of 17α-bromo-6α-methylprogesterone (XII). The introduction of a methyl substituent in position 6α appeared of particular interest in view of the observation that this group exerted, in a number of instances, a drastic potentiating effect on the *oral* progestational activity (cf. refs. 7–11).[5]

Pregnenolone acetate (I) served as starting material. It was transformed, in high yield, to the 20-ethylene ketal (II) (14) by slow evaporation of its solution in ethylene glycol in the presence of *p*-toluenesulphonic acid, according to the procedure of Allen *et al.* (15). The use of the classical method which was employed by Gut (14) and which consists in refluxing the benzene solution of the ketone with ethylene glycol in the presence of *p*-toluenesulphonic acid, with periodic removal of water, gives less satisfactory yields of the desired ketal.[6] Epoxidation of the unsaturated acetoxy ketal II*a* with monoperphtalic acid in chloroform afforded predominantly the α-epoxide III, as expected. The product gave no tetranitromethane reaction and the analytical data and spectral characteristics were in accord with structure III. The α-configuration was not only assigned in analogy with data from the literature (cf., e.g., refs. 16–19; also refs. 20 and 21) but was also

[1]*The main results of this paper were the subject of a communication presented before the 43rd Annual Conference of the Chemical Institute of Canada, June 1960.*
[2]*For the previous paper in this series, see ref. 1.*
[3]*Correspondence should be addressed to this author.*
[4]*Subsequent to our publication, Mills, Candiani, and Djerassi (6) also published a synthesis of 6α-fluoro-17α-bromoprogesterone, without indicating the progestational activity of the product.*
[5]*In this respect it may be mentioned that after completion of this work one of us (R. D.) established, in collaboration with R. Gaudry, that the addition of a 6α-methyl substituent transformed the parenterally potent but orally almost inactive 17α-methylprogesterone (12) to an orally active progestin (13).*
[6]*Unpublished results from our laboratory by R.-M. Hoegerle and Ch. R. Engel.*



proved by the conversion of the epoxide III, with lithium aluminum hydride, to the 3β,5α-dihydroxy ketal VII, and hence, by an exchange reaction with acetone in the presence of *p*-toluenesulphonic acid (22), to the known (23) 3β,5α-dihydroxypregnan-20-one (VI).

In an attempt to isolate, out of the crude epoxidation product, the isomeric 5β,6β-epoxide IV—the formation of which was to be expected (cf. refs. 17, 18, and 20)—we subjected the mother liquors which remained after the separation of the α-epoxide III and of intermediate fractions to chromatography on non-alkaline aluminum oxide "Woelm". Apart from small quantities of the α-epoxide III, the only product which could be isolated in the pure state (by recrystallization of the less-polar chromatogram fractions) was an isomer of the oxide III, to which we assign the structure of 3β-acetoxy-20-ethylenedioxy-5α-pregnan-6-one (VIII*a*) since its infrared spectrum shows the band of a 6-membered-ring ketone. (The retention of the ketal function in position 20 was evident from the infrared spectrum and the analytical data.) Also, upon saponification with methanolic sodium hydroxide, there remains only a single ketonic carbonyl band, attributable to the 6-keto function (ν_{max}^{KBr} 1715 cm^{-1}) (cf. VIII), and reacetylation of the saponified product leads back to the acetoxy ketone VIII*a*, which has two distinct carbonyl-absorption bands (ν_{max}^{KBr} 1741 and 1713 cm^{-1}). Since the crude epoxidation product shows practically no carbonyl absorption in the infrared, we assume that the 5β,6β-epoxide, originally formed as the minor epoxidation product, was isomerized in the course of chromatography on the particular brand of aluminum oxide used (Woelm) to the 6-ketone. Such rearrangements are known to occur under the influence of Lewis acids (24, 25) and can be rationalized readily by assuming that, initially, the C—O bond is ionized at the most substituted carbon atom and that, subsequently, a cis hydrogen shift occurs. We thus suggest the 5α-configuration for the ketones VIII and VIII*a*. The assumption that the ketone arises from the 5β,6β-epoxide and not from the α-epoxide was substantiated by the fact that chromatography (on the same brand of aluminum oxide) of the α-epoxide III resulted in the quantitative recovery of unchanged α-epoxide. Henbest and Wrigley have already shown (24) that 5β,6β-epoxides are more prone to rearrangement to 6-ketones than the corresponding 5α,6α-epoxides.

Treatment of the acetoxy ethylenedioxy α-epoxide III with an excess of methyl magnesium bromide gave the 3β,5α-dihydroxy 6β-methyl ketal V in 50% yield. Deketalization with acetone and *p*-toluenesulphonic acid (22) afforded 3β,5α-dihydroxy-6β-methylpregnan-20-one (IX), which was converted directly to the acetate IX*a*. The structure of the intermediates V, IX, and IX*a* was confirmed by oxidation, with chromic acid and sulphuric acid in acetone (26, 27), of the dihydroxy ketone IX to the known (28, 29) 5α-hydroxy-6β-methylpregnane-3,20-dione (XIII). Since this diketone XIII is readily converted to 6α-methylprogesterone (XIV) (and also to its 6β-epimer) (28, 29, cf. also Experimental), the sequence of reactions described above represents a new and useful variation of the synthesis of 6-methylated progesterones from pregnenolone or pregnenolone acetate. In our syntheis, we protect the 20-keto function against the action of the Grignard reagent by the formation of a 20-ketal, while the British authors (29) reduce the 20-ketone to a mixture of epimeric 20-alcohols, which they acetylate prior to the Grignard reaction; the authors from Mexico (28) use a homogeneous, but less readily available, 3β,20β-diacetoxy derivative as starting material.

In pursuance of our main objective, we brominated 3β-acetoxy-5α-hydroxy-6β-methylpregnan-20-one (IX*a*) with N-bromosuccinimide under illumination (cf. refs. 30 and 3) and thus obtained the 17α-bromo adduct X*a*. Particularly rewarding results were achieved when a small amount of a tertiary base, such as pyridine, was added to the reaction mixture (cf. ref. 5). Since the acetoxy bromide X*a* is not readily purified, it was hydrolyzed directly to 17α-bromo-3β,5α-dihydroxy-6β-methylpregnan-20-one (X) with perchloric acid in methanol (2, 31). The resulting hydroxy bromide X was purified by chromatography

and recrystallization; the yield of pure bromide X from the acetoxy hydroxy ketone IX*a* amounted to 57%. Upon bromination in position 17α, the typical levorotatory shift (2, 3, 12, 32) was observed. The location of the bromine substituent could be anticipated from analogous reactions (cf. refs. 2, 3, and 30) and was proved by the conversion of the final product, 17α-bromo-6α-methylprogesterone (XII), to 16-dehydro-6α-methylprogesterone (XV), as described below. The α-configuration of the 17-halogen substituent follows from the fact that a free-radical bromination of a 20-ketone affords the same stereoisomer as an acid-catalyzed bromination (cf., e.g., refs. 32 and 33), which leads exclusively to the 17α-bromo derivative (34).

The hydroxy keto bromide X was oxidized, in high yield, with chromic acid and sulphuric acid in acetone (26, 27) to 17α-bromo-5α-hydroxy-6β-methylpregnane-3,20-dione (XI). Dehydration with concomitant epimerization in position 6, leading to the desired 17α-bromo-6α-methylprogesterone (XII), was achieved in good yield by treatment with hydrogen chloride in acetic acid (cf. refs. 3 and 19). The structure and the stereochemistry of the skeleton were proved by reduction of the progesterone derivative XII, with zinc and acetic acid, to 6α-methylprogesterone (XIV) (28, 29)[7] and was further confirmed by dehydrobromination with dimethylformamide and lithium chloride (cf. ref. 35) to the known (29) 16-dehydro-6α-methylprogesterone (XV). This last reaction also constitutes a proof of the location of the bromine substituent.

According to preliminary biological tests—for which we are indebted to Dr. E. G. Shipley of the Endocrine Laboratories of Madison, Inc., Madison, Wisc., and to Drs. J. Tripod and P. Desaulles of Ciba Ltd., Basle, Switzerland—17α-bromo-6α-methylprogesterone is a potent progestin which considerably exceeds in activity not only the natural hormone of the *corpus luteum* but also 17α-bromoprogesterone, both upon parenteral and oral administration.[8] The enhancing effect of the bulky 17α-bromine substituent on progestational activity (cf. refs. 2–4) is thus further substantiated. The implications of the establishment of high progestational activity of 17α-brominated progestins on activity–structure relationships will be discussed elsewhere on a broader basis.

EXPERIMENTAL[9, 10, 11]

Δ^5-3β-Acetoxy-20-ethylenedioxypregnene (IIa) (14)

Following the procedure of Allen *et al.* (15), 20 g of Δ^5-3β-acetoxypregnen-20-one (I) was ketalized with ethylene glycol in the presence of *p*-toluenesulphonic acid, by slow distillation of ethylene glycol, at 72–75° and 2 mm Hg pressure. The infrared spectrum of the reaction product revealed that hydrolysis in position 3 had occurred. The usual acetylation with acetic anhydride in pyridine at room temperature afforded 20.6 g of semicrystalline acetoxy ketal II*a*, which gave, upon crystallization from ether–methanol, 18.01 g of pure ketal II*a*, m.p. 156–158°, and a second batch of 600 mg, melting between 152 and 154° (yield of pure product 83%). A sample was recrystallized once from methanol for analysis; colorless scales; m.p. 159–161°; $[\alpha]_D^{24}$ −41.5° (*c*, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1740 and 1250 cm^{-1} (acetate), 1042 cm^{-1} (20-ketal). Anal. Calc. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.30; H, 9.35.

5α,6α-Epoxy-3β-acetoxy-20-ethylenedioxypregnane (III) and 3β-Acetoxy-20-ethylenedioxy-5α-pregnan-6-one (VIIIa)

To a solution of 38.5 g of Δ^5-3β-acetoxy-20-ethylenedioxypregnene (II*a*), m.p. 156–158°, in 1.9 liters of chloroform, there was added, at −80°, over a period of 20 minutes, 520 cc of a 0.4 *N* ethereal monoperphtalic

[7] *We sincerely thank Dr. V. Petrow for an authentic sample of 6α-methylprogesterone.*
[8] *A detailed report on the biological effects of 17α-bromo-6α-methylprogesterone will appear elsewhere.*
[9] *The melting points were taken in evacuated capillaries and the temperatures were corrected.*
[10] *If not otherwise stated, Woelm's non-alkaline aluminum oxide and Davison's silica gel No. 923 were used for chromatography.*
[11] *The microanalyses were performed by Dr. O. Schwarzkopf, New York, N.Y.; Dr. C. Daesslé, Montreal, Quebec; Mr. J. F. Alicino, Metuchen, N.J.; and Mr. A. Bernhardt, Mülheim (Ruhr), Germany, and their associates, to whom we express our sincere appreciation.*

acid solution. The mixture was kept at −80° for 2 hours, and between 0 and 5° for another 16 hours. Subsequently, the solution was washed with a cold 5% sodium carbonate solution and with water and was dried over sodium sulphate. Removal of the solvent gave 41.2 g of crude crystalline material which yielded, upon recrystallization from ether–methanol containing a few drops of pyridine, 27.06 g (67.6%) of pure *5α,6α-epoxy-3β-acetoxy-20-ethylenedioxypregnane (III)*, m.p. 183–185°. The infrared spectrum revealed no significant carbonyl absorption. A portion of this product was recrystallized once from ether–methanol for analysis; colorless needles; m.p. 184–186°; $[\alpha]_D^{25}$ −50° (*c*, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1740 and 1250 cm^{-1} (acetate), 1042 cm^{-1} (ketal). Anal. Calc. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.54; H, 9.02.

From the mother liquors of the first crystallization two further batches of crystals were isolated: a first crop of 1.457 g, m.p. 154–161°, $[\alpha]_D^{24}$ −33.3° (*c*, 1.000 in $CHCl_3$), and a second crop of 1.04 g, m.p. 104–108°, $[\alpha]_D^{24}$ −5.9° (*c*, 1.000 in $CHCl_3$). The remaining mother liquors (10.1 g) were absorbed on 300 g of aluminum oxide Woelm, activity III, pH 7.5–8. Elutions with petroleum ether – benzene (4:1) afforded 5.199 g of crystals, m.p. 109–112°, $[\alpha]_D^{23}$ −5°; petroleum ether – benzene (1:1) eluted at first 2.316 g of crystals melting between 104 and 115°, $[\alpha]_D^{23}$ −6°, and subsequently 2.285 g of a crystalline product, representing a crude mixture and melting between 130 and 173°, with specific rotations ranging from −20.5 to −35°. The last petroleum ether – benzene (1:1) eluates represented 265 mg (0.66%) of pure α-epoxide III, m.p. 181–184°, $[\alpha]_D^{24}$ −46°, identified by mixed melting point and infrared analysis. The fractions with a specific rotation of −5 to −6° (7.5 g) showed in the infrared a ketonic carbonyl absorption and represented crude *3β-acetoxy-20-ethylenedioxy-5α-pregnan-6-one (VIIIa)*. They were recrystallized four times from ether for analysis; colorless plates; m.p. 141–143°; $[\alpha]_D^{24}$ −12.5° (*c*, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1741 cm^{-1} (acetate), 1713 cm^{-1} (6-ketone), 1250 cm^{-1} (acetate), 1040 cm^{-1} (ketal). Anal. Calc. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 72.00; H, 9.07.

Saponification and Reacetylation

To a solution of 110 mg of the above-described 6-ketone VIII*a*, m.p. 140–142°, in 50 cc of methanol was added 2 cc of a 2 *N* sodium hydroxide solution. The mixture was refluxed for 7.5 hours and subsequently the volume of the solution was reduced, *in vacuo*, to 10 cc. The product was poured into cold water and the precipitate was extracted with ether. The ethereal solution was washed with water and was dried over sodium sulphate. Removal of the solvent afforded 100 mg of an amorphous product representing crude *hydroxy keto ketal VIII*, ν_{max}^{KBr} 1715 cm^{-1} (6-ketone), 1050 cm^{-1} (ketal). Upon reacetylation with 0.5 cc of acetic anhydride in 1 cc of pyridine, at room temperature, over a period of 16 hours, there was obtained 108 mg of crystalline ketone VIII*a*, which melted after one recrystallization from ether at 140–142°. The identity with the product isolated from the epoxidation mixture was established by a mixed melting point determination and infrared analysis.

Chromatography of Epoxide III

A quantity of 1 g of 5α,6α-epoxide III, m.p. 181–183°, was chromatographed on 40 g of non-alkaline aluminum oxide Woelm, activity III. Petroleum ether – benzene mixtures (4:1, 1:1, and 1:4) eluted 1 g of the 5α,6α-epoxide III; the melting points of the various fractions ranged from 180 to 184°. The product was in every respect identical with the starting material.

In other runs, there were obtained 10 g of α-epoxide III, m.p. 183–184°, from 14.05 g of ketal II*a* (68.4% yield) and 7.945 g of epoxide III, m.p. 178–184°, from 10 g of ketal II*a* (76.4% yield).

3β,5α-Dihydroxypregnan-20-one (VI)

A solution of 200 mg of 5α,6α-epoxy-3β-acetoxy-20-ethylenedioxypregnane (III), m.p. 181–183°, in 20 cc of absolute tetrahydrofuran was added, with stirring, to a slurry of 200 mg of lithium aluminum hydride in 100 cc of tetrahydrofuran. The mixture was refluxed for 1 hour with exclusion of moisture and was left for another 16 hours at room remperature. The excess reagent was decomposed by careful addition of moist ethyl acetate. Ice water was added and the mixture was extracted with ether. The organic layer was washed with iced dilute sulphuric acid, cold sodium bicarbonate solution, and with water and was dried over sodium sulphate. Removal of the solvent afforded 175 mg of a product representing crude *3β,5α-dihydroxy-20-ethylenedioxypregnane (VII)*; m.p. 217–222°; ν_{max}^{KBr} 3400 cm^{-1} (3β-hydroxyl), 3280 cm^{-1} (5α-hydroxyl), 1046 cm^{-1} (ketal). The product was dissolved without further purification in 10 cc of methanol and was treated for 1 hour, at reflux temperature, with 2 cc of an 8% sulphuric acid solution. The mixture was cooled and poured into a sodium bicarbonate solution. The precipitate was extracted with ether, the ethereal solution was washed with water and was dried over sodium sulphate. Removal of the solvent afforded 130 mg of 3β,5α-dihydroxypregnan-20-one (VI), m.p. 222–226°. A sample was recrystallized once from ethyl acetate – methanol and once from methanol, and was finally sublimed at 175° for analysis; prisms; m.p. 232–234°; $[\alpha]_D^{24}$ +105° (*c*, 1.000 in $CHCl_3$); ν_{max}^{KBr} 3480 cm^{-1} (3β-hydroxyl), 3450 cm^{-1} (partly associated 5α-hydroxyl), 1690 cm^{-1} (20-ketone). Anal. Calc. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.14; H, 10.00.

3β,5α-Dihydroxy-20-ethylenedioxy-6β-methylpregnane (V)

To an ethereal Grignard solution prepared from 1.5 g of magnesium and a slight excess of methyl bromide there was added a solution of 3 g of 5α,6α-epoxy-3β-acetoxy-20-ethylenedioxypregnane (III), m.p. 183–185°, in 450 cc of absolute benzene. The reaction mixture was refluxed for 4 hours, and, after cooling, the excess

reagent was decomposed with an aqueous solution of ammonium chloride. The organic layer was washed with an aqueous ammonium chloride solution and with water and was dried over sodium sulphate. Removal of the solvent afforded 2.9 g of a solid which was chromatographed on 80 g of aluminum oxide, activity III, pH 7.5. Elutions with benzene–ether mixtures (4:1 and 1:1) and with pure ether afforded 1.4 g (50%) of 3β,5α-dihydroxy-20-ethylenedioxy-6β-methylpregnane (V), m.p. 162–164°. A sample was recrystallized twice, from ether, for analysis; fine needles; m.p. 168.5–169.5°; $[\alpha]_D^{25}$ −32° (*c*, 0.900 in $CHCl_3$); ν_{max}^{KBr} 3450 cm^{-1} (3β-hydroxyl), 3380 cm^{-1} (5α-hydroxyl), 1045 cm^{-1} (20-ketal). Anal. Calc. for $C_{24}H_{40}O_4$: C, 73.42; H, 10.27. Found: C, 73.63; H, 9.91.

3β-Acetoxy-5α-hydroxy-6β-methylpregnan-20-one (IXa)

A solution of 1.3 g of 3β,5α-dihydroxy-20-ethylenedioxy-6β-methylpregnane (V), m.p. 162–164°, and of 175 mg of *p*-toluenesulphonic acid in 100 cc of absolute acetone was refluxed for 1 hour. The volume of the solution was reduced *in vacuo* to approximately 25 cc and the product was poured into an iced sodium bicarbonate solution. The precipitate was extracted with dichloromethane, the organic solution was washed with water and was dried over sodium sulphate. Removal of the solvent afforded 1.2 g of crude *3β,5α-dihydroxy-6β-methylpregnan-20-one (IX)*, which was acetylated in the usual fashion with 1 cc of acetic anhydride in 4 cc of pyridine at room temperature, for a period of 16 hours. The usual working up afforded 1.15 g of a solid which, upon recrystallization from acetone–ether, gave 800 mg of pure *3β-acetoxy-5α-hydroxy-6β-methylpregnan-20-one (IXa)*, m.p. 195–197°. Chromatography of the mother liquors on aluminum oxide gave another 240 mg of the same product (total yield 80%). A sample was recrystallized once from acetone–ether for analysis; prisms; m.p. 198–200°; $[\alpha]_D^{24}$ +29.6° (*c*, 0.950 in $CHCl_3$); ν_{max}^{KBr} 3500 cm^{-1} (5α-hydroxyl), 1745 cm^{-1} (acetate), 1705 cm^{-1} (20-ketone), 1250 cm^{-1} (acetate). Anal. Calc. for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.69, 73.83; H, 9.60, 9.77.

In another run, 14.91 g of ketal V was transformed in a similar manner to 12.2 g of acetoxy ketone IX*a*, m.p. 192–193° (82% yield).

3β,5α-Dihydroxy-6β-methylpregnan-20-one (IX)

A solution of 100 mg of 3β-acetoxy-5α-hydroxy-6β-methylpregnan-20-one (IX*a*) in 15 cc of methanol and 0.75 cc of 70% perchloric acid was kept at room temperature for 20 hours. The product was poured into an iced sodium bicarbonate solution and the precipitate was extracted with dichloromethane. The organic solution was washed until neutral, dried over sodium sulphate, and taken to dryness. The resulting product (90 mg), representing *3β,5α-dihydroxy-6β-methylpregnan-20-one (IX)*, crystallized from ether; m.p. 186–187°; ν_{max}^{KBr} 3450 cm^{-1} (broad 3β,5α-dihydroxy band), 1707 cm^{-1} (20-ketone).

In another run, 4 g of acetate IX*a* was hydrolyzed in a similar manner to yield 3.2 g of purified dihydroxy ketone IX, m.p. 186–187°. The material was not further purified and was used directly in the following reaction.

5α-Hydroxy-6β-methylpregnane-3,20-dione (XIII) (cf. refs. 28 and 29)

To a solution of 160 mg of the dihydroxy ketone IX in 10 cc of absolute acetone there was added, dropwise and with stirring, at 0–5°, an oxidizing solution prepared by dissolving 267 mg of chromic acid in 230 cc of concentrated sulphuric acid and 770 cc of water. The addition was continued until the solution remained light brown. The mixture was stirred for another 3 minutes and was poured subsequently into ice water. The precipitate was collected, washed, and dried. The resulting 150 mg of crude material was absorbed on 5 g of aluminum oxide, Merck, activity II–III, pH 7.0, prepared as described under footnote 31 of reference 36. Methylene chloride and methylene chloride – acetone (4:1) eluted 55 mg of crystalline hydroxy diketone XIII. The product was recrystallized once from acetone–ether for analysis; needles; m.p. 250–252°; ν_{max}^{KBr} 3400 cm^{-1} (5α-hydroxyl), 1710 cm^{-1} (broad 3,20-diketo band). Anal. Calc. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.85. Found: C, 76.20; H, 9.70.

In another run, 3.2 g of the dihydroxy ketone IX was oxidized in a similar fashion and gave 2.811 g of crude crystalline hydroxy diketone XIII, m.p. 230–235°, contaminated with some dehydrated product. This material was transformed directly to 6α-methylprogesterone (XIV) (cf. below).

17α-Bromo-3β,5α-dihydroxy-6β-methylpregnan-20-one (X)

A solution of 1.0 g of 3β-acetoxy-5α-hydroxy-6β-methylpregnan-20-one (IX*a*) in 80 cc of absolute carbon tetrachloride was refluxed for 10 minutes with 456 mg of N-bromosuccinimide and 0.2 cc of pyridine, over a photoflood lamp. The mixture was cooled and filtered through sodium sulphate, the sodium sulphate was washed with carbon tetrachloride, and the original solution and the washings were combined. The resulting solution was washed with iced 10% sodium bisulphite solution, iced bicarbonate solution, and with water and was dried over sodium sulphate. Removal of the solvent *in vacuo* afforded 1.21 g of a yellow foam which did not crystallize readily and which represented crude *17α-bromo-3β-acetoxy-5α-hydroxy-6β-methylpregnan-20-one (Xa)*. The product was not further purified and was hydrolyzed as follows.

A quantity of 1.2 g of the above-described crude acetoxy bromide X*a* was subjected, for 22 hours, to the action of 7.5 cc of 70% perchloric acid in 180 cc of methanol. Subsequently, the solution was poured into an iced sodium bicarbonate solution and the precipitate was extracted with methylene chloride. The organic layer was washed with water and was dried over sodium sulphate. Removal of the solvent *in vacuo* afforded

1.05 g of an amorphous product. The material was dissolved in a small quantity of benzene and absorbed on 100 g of silica gel. Elutions with benzene – ethyl acetate (4:1) afforded 620 mg (56.6% yield from ketone IX*a*) of crystalline *17α-bromo-3β,5α-dihydroxy-6β-methylpregnan-20-one (X)*, m.p. 151–153° decomp. A sample was recrystallized three times from ether–hexane for analysis; small needles; m.p. 155–156° decomp.; $[\alpha]_D^{26}$ −68.0° (*c*, 0.750 in $CHCl_3$); ν_{max}^{KBr} 3450 cm^{-1} (3β-hydroxyl), 3350 cm^{-1} (5α-hydroxyl), 1709 cm^{-1} (20-ketone). Anal. Calc. for $C_{22}H_{35}O_3Br$: C, 61.82; H, 8.25; Br, 18.70. Found: C, 61.70, 61.66; H, 8.00, 8.56; Br, 18.48, 18.99.

17α-Bromo-5α-hydroxy-6β-methylpregnane-3,20-dione (XI)

To a solution of 600 mg of 17α-bromo-3β,5α-dihydroxy-6β-methylpregnan-20-one (X), m.p. 151–153° decomp., in 40 cc of absolute acetone there was added, at 0–5°, 0.9 cc of the previously described chromic acid solution in dilute sulphuric acid. The mixture was stirred for 3 minutes and was poured into an iced sodium bicarbonate solution. The precipitate was extracted with dichloromethane and the organic layer was washed with water and was dried over sodium sulphate. Removal of the solvent *in vacuo* afforded 580 mg of a semicrystalline solid which, upon crystallization from acetone–ether, gave 400 mg of 17α-bromo-5α-hydroxy-6β-methylpregnane-3,20-dione (XI), m.p. 168–170° decomp. The mother liquors were chromatographed on 18 g of silica gel. Elutions with benzene – ethyl acetate (96:4) gave another 150 mg of the bromo diketone XI, m.p. 168–170° decomp. (total yield 92%). A sample was recrystallized once from ether–acetone for analysis; fine needles; m.p. 170–171° decomp.; $[\alpha]_D^{26}$ −49.9° (*c*, 0.850 in $CHCl_3$); ν_{max}^{KBr} 3450 cm^{-1} (5α-hydroxyl), 1707 cm^{-1} (broad 3,20-diketo band). Anal. Calc. for $C_{22}H_{33}O_3Br$: C, 62.11; H, 7.82; Br, 18.78. Found: C, 62.36, 61.95; H, 8.01, 7.84; Br, 19.00, 19.08.

Δ⁴-17α-Bromo-6α-methylpregnene-3,20-dione (17α-Bromo-6α-methylprogesterone) (XII)

Through a solution of 500 mg of 17α-bromo-5α-hydroxy-6β-methylpregnane-3,20-dione (XI), m.p. 168–170° decomp., in 100 cc of acetic acid, there was passed, at 10° and for 2 hours, a stream of dry hydrogen chloride. Subsequently, the solution was kept for 16 hours at 0–5° and was then poured into an iced sodium chloride solution. The precipitate was extracted with ether, the ethereal solution was washed with ice water, with iced sodium bicarbonate solution, and with water and was dried over sodium sulphate. Upon removal of the solvent *in vacuo* 450 mg of a semicrystalline material was obtained. The product was absorbed on 45 g of silica gel. Elutions with benzene – ethyl acetate (97:3) gave 280 mg (58.5% yield) of 17α-bromo-6α-methylprogesterone (XII), m.p. 149–151° decomp. A sample was recrystallized four times from ether–hexane for analysis; colorless prisms; m.p. 153–154° decomp.; $[\alpha]_D^{24}$ +10.2° (*c*, 1.580 in $CHCl_3$); λ_{max}^{EtOH} 237 mμ (log ε 4.19); ν_{max}^{KBr} 1703 cm^{-1} (20-ketone), 1672 and 1610 cm^{-1} (Δ⁴-3-keto doublet). Anal. Calc. for $C_{22}H_{31}O_2Br$: C, 64.86; H, 7.67; Br, 19.62. Found: C, 64.97, 64.62; H, 7.80, 7.72; Br, 19.89, 19.77.

Δ⁴-6α-Methylpregnene-3,20-dione (6α-Methylprogesterone) (XIV) (cf. refs. 28 and 29)

(a) From 5α-Hydroxy-6β-methylpregnane-3,20-dione (XIII)

Through a solution of 2.5 g of crude, partly dehydrated 5α-hydroxy-6β-methylpregnane-3,20-dione (XIII), obtained by oxidation of the dihydroxy ketone IX (see above), in 100 cc of acetic acid, there was passed, at 10–15°, for 2 hours, a stream of dry hydrogen chloride. The product was further treated and worked up as described for the preparation of 17α-bromo-6α-methylprogesterone (XII) (see above). Thus, 2 g of crude 6α-methylprogesterone (XIV), λ_{max}^{EtOH} 241 mμ (log ε 4.08), was obtained. Chromatography on 60 g of aluminum oxide, activity III, afforded 1.6 g (67.5% yield) of 6α-methylprogesterone (XIV), m.p. 119–122°, $[\alpha]_D^{23}$ +172° (*c*, 0.850 in $CHCl_3$). The infrared spectrum of the product was identical with that of an authentic sample of 6α-methylprogesterone, kindly supplied by Dr. V. Petrow,[7] and no depression of melting point was observed upon mixture of the two samples.

(b) From 17α-Bromo-6α-methylprogesterone (XII)

To a solution of 30 mg of 17α-bromo-6α-methylprogesterone (XII) in 10 cc of acetic acid there was added, at 80°, portionwise and with shaking, 500 mg of zinc dust. The mixture was heated with intermittent shaking for another 2 hours on a boiling water bath. The reaction mixture was cooled, diluted with ether, and filtered. The filtrate was further diluted with ether and the ethereal solution was washed with dilute hydrochloric acid, water, sodium bicarbonate solution, and with water and was dried over sodium sulphate. Evaporation of the solvent afforded 20 mg of an amorphous product which crystallized from acetone–hexane. Thus, 14 mg of 6α-methylprogesterone (XIV), m.p. 121–123°, $[\alpha]_D^{25}$ +176° (*c*, 0.600 in $CHCl_3$), λ_{max}^{EtOH} 241 mμ (log ε 4.19), was obtained. The identity of this product with authentic 6α-methylprogesterone[7] was established by a mixed melting point and by the comparison of the infrared spectra.

Δ⁴,¹⁶-6α-Methylpregnadiene-3,20-dione (6α-Methyl-16-dehydroprogesterone) (XV) (29)

A solution of 60 mg of 17α-bromo-6α-methylprogesterone (XII), m.p. 150–152° decomp., in 15 cc of dimethylformamide was refluxed, in a nitrogen atmosphere, with 12 mg of lithium chloride, for 1 hour. Subsequently, the mixture was cooled and extracted with ether. The ethereal solution was washed with dilute hydrochloric acid, water, sodium bicarbonate solution, and again with water and was dried over sodium sulphate. Removal of the solvent afforded 45 mg (93.6% yield) of crude, crystalline 6α-methyl-16-dehydroprogesterone (XV), m.p. 172–175°. The product was absorbed on a column of 2 g of silica gel and

eluted with benzene – ethyl acetate (97:3). Thus, 30 mg (62.4%) of colorless crystals, m.p. 174–176°, were obtained. The product was recrystallized twice from ether for analysis; prisms; m.p. 180–182°; $[\alpha]_D^{24}$ +153° (*c*, 0.650 in $CHCl_3$); λ_{max}^{EtOH} 240 mμ (log ε 4.46); ν_{max}^{KBr} 1670 and 1610 cm^{-1} (Δ^4-3-keto doublet), 1661 cm^{-1} (shoulder), 1590 cm^{-1} (Δ^{16}-20-keto doublet). Anal. Calc. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.54; H, 9.22.

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REFERENCES

1. S. Rakhit and Ch. R. Engel. Can. J. Chem. **40**, 2163 (1962).
2. Ch. R. Engel and H. Jahnke. Can. J. Biochem. Physiol. **35**, 1047 (1957).
3. Ch. R. Engel and R. Deghenghi. Can. J. Chem. **38**, 452 (1960).
4. Ch. R. Engel. Abstracts, 1st International Congress of Endocrinology, Copenhagen. 1960. p. 913.
5. D. J. Marshall and R. Gaudry. Can. J. Chem. **38**, 1495 (1960).
6. J. S. Mills, O. Candiani, and C. Djerassi. J. Org. Chem. **25**, 1056 (1960).
7. A. David, F. Hartley, D. R. Millson, and V. Petrow. J. Pharm. Pharmacol. **9**, 929 (1957).
8. J. A. Campbell, J. C. Babcock, and J. A. Hogg. J. Am. Chem. Soc. **80**, 4717 (1958).
9. J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin. J. Am. Chem. Soc. **80**, 2904 (1958).
10. H. J. Ringold, J. P. Ruelas, E. Batres, and C. Djerassi. J. Am. Chem. Soc. **81**, 3712 (1959).
11. P. B. Sollman, R. L. Elton, and R. M. Dodson. J. Am. Chem. Soc. **81**, 4435 (1959).
12. H. Heusser, Ch. R. Engel, P. Th. Herzig, and Pl. A. Plattner. Helv. Chim. Acta, **33**, 2229 (1950).
13. R. Deghenghi and R. Gaudry. J. Am. Chem. Soc. **83**, 4668 (1961).
14. M. Gut. J. Org. Chem. **21**, 1327 (1956).
15. W. S. Allen, S. Bernstein, and R. Littell. J. Am. Chem. Soc. **76**, 6116 (1954).
16. L. Ruzicka and W. Bosshard. Helv. Chim. Acta, **20**, 244 (1937).
17. Pl. A. Plattner, Th. Petrzilka, and W. Lang. Helv. Chim. Acta, **27**, 513 (1944).
18. L. Ruzicka and A. C. Muhr. Helv. Chim. Acta, **27**, 503 (1944).
19. A. Bowers and H. J. Ringold. Tetrahedron, **3**, 14 (1958).
20. M. Ehrenstein. J. Org. Chem. **6**, 626 (1941).
21. M. Ehrenstein and Th. O. Stevens. J. Org. Chem. **6**, 908 (1941).
22. H. Schinz and G. Schäppi. Helv. Chim. Acta, **30**, 1483 (1947).
23. S. Julia. Ann. Chim. France, **8**, 410 (1953).
24. H. B. Henbest and T. I. Wrigley. J. Chem. Soc. 4596 (1957).
25. H. B. Henbest and T. I. Wrigley. J. Chem. Soc. 4765 (1957).
26. K. Bowden, J. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon. J. Chem. Soc. 39 (1946).
27. C. Djerassi, R. R. Engle, and A. Bowers. J. Org. Chem. **21**, 1547 (1956).
28. H. J. Ringold, E. Batres, and G. Rosenkranz. J. Org. Chem. **22**, 99 (1957).
29. D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson. J. Chem. Soc. 4092 (1957).
30. R. U. Shock and W. J. Karpel. U.S. Patent No. 2,684,963 (1954).
31. J. Fried and F. Sabo. J. Am. Chem. Soc. **79**, 1130 (1957).
32. R. Deghenghi and Ch. R. Engel. J. Am. Chem. Soc. **82**, 3201 (1960).
33. Ch. R. Engel, G. Just, and R. Buttery. Can. J. Chem. **39**, 1805 (1961).
34. N. L. Wendler, R. P. Graber, and G. G. Hazen. Tetrahedron, **3**, 144 (1958).
35. R. P. Holysz. J. Am. Chem. Soc. **75**, 4432 (1953).
36. Ch. R. Engel and G. Just. J. Am. Chem. Soc. **76**, 4909 (1954).