solvents under reduced pressure left a colorless oil which solidified upon trituration with 5% aqueous sodium bicarbonate. From 0.35 g. of XXVa there was obtained 0.31 g. (98%) of crude 16α-hydroxy-cevanidane-3-one (XXVIa); two recrystallizations from ethanol–water gave a pure sample, m.p. 207.5–210°, $[\alpha]^{25}D$ −42.7° (*c* 1.28, $CHCl_3$). A mixture m.p. with 18-hydroxysolanidane-3-one (XIIa), m.p. 217–220°, was depressed.

Anal. Calcd. for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 78.31; H, 10.54; N, 3.80.

The acetate was prepared by the pyridine–acetic anhydride procedure; m.p. 163–167.5° after recrystallization from acetone–water, $[\alpha]^{24}D$ −44° (*c* 1.22, pyridine). A mixture m.p. with 18-acetoxysolanidane-3-one, m.p. 174–176.5°, was depressed.

Anal. Calcd. for $C_{29}H_{45}NO_3$: C, 76.44; H, 9.95; N, 3.07. Found: C, 76.33; H, 9.90; N, 3.26.

Cevanidane-3,16-dione (XXVII).—To a solution of 0.11 g. of 16α-hydroxycevanidane-3-one (XXVIa) in 15 ml. of acetone there was added sufficient Kiliani reagent[20] to give a permanent orange color. Addition of a few drops of water gave a green oily phase which was removed by filtration through Celite. The filtrate was made basic with *N* aqueous sodium hydroxide and was diluted with water; an oil separated which solidified upon trituration to give a quantitative yield of cevanidane-3,16-dione (XXVII). Recrystallization from acetone–water gave pure material, m.p. 158–161°, $[\alpha]^{24}D$ −84° (*c* 1.02, pyridine), ν_{max}^{KBr} 1740 and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.66; H, 10.15; N, 3.67.

Hofmann Degradation of Isorubijervine Monotosylate.—Isorubijervine monotosylate (XXVIII)[3b] was added to a solution of 1 g. of potassium in 20 ml. of *t*-butyl alcohol. After heating the solution under reflux for 16 hours, the product was isolated by diluting the reaction mixture with water and extracting with methylene chloride. Removal of solvent from the extracts afforded 97 mg. (69%) of 3β-hydroxy-5,15-cevanidiene (XXXI), m.p. 227–230° after crystallization from acetone.

Anal. Calcd. for $C_{27}H_{40}NO$: C, 81.97; H, 10.45; N, 3.54. Found: C, 81.80; H, 10.36; N, 3.54.

Hydrogenation of 60.6 mg. of this material in glacial acetic acid over Adams catalyst gave 25 mg. of 3β-hydroxycevanidane (XXIX), m.p. 209–213°, $[\alpha]D$ + 32.5° (*c* 0.55, $CHCl_3$). Two moles of hydrogen was consumed during the reduction. A mixture m.p. with 3β-hydroxycevanidane prepared from 18-oxocevanidane-3-one (XXIV) was undepressed.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PRODUCTOS ESTEROIDES, S. A. DE C. V.]

Synthesis of 6-Methyl Steroids

BY LUIS MIRAMONTES, PASCUAL AGUINACO AND MIGUEL A. ROMERO

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A facile synthesis of 6α-methylprogesterone and 6α-methyl-17α-hydroxyprogesterone has been developed. A novel feature of the method involves the simultaneous attack at the nitrile and epoxide groups by methylmagnesium bromide on 5α,6α-epoxy-17-cyano-16-androsten-3β-ol acetate (III).

The introduction of a methyl substituent at the C-6 position of the steroid nucleus and the resulting enhancement of physiological properties has been the subject of several communications[1] during the past three years.

In all cases except that of the oxo reaction[1e,1f] the 6-methyl group has been introduced either by cleavage of the corresponding 5α,6α-epoxide with methylmagnesium halide or by adding this reagent to the 6-keto derivative. The nature of such a reaction imposes certain restrictions on its use, since any other substituents subject to attack by the Grignard reagent must be protected. The provision and removal of such protective groups has been a handicap in the synthesis of 6-methyl progestational and cortical steroids.

Petrow[1c] circumvented this problem in the synthesis of 6-methylprogesterone by treating the 5α,6α-epoxide of diosgenin with the Grignard reagent and degrading the adduct by normal procedures (the yield was not reported).

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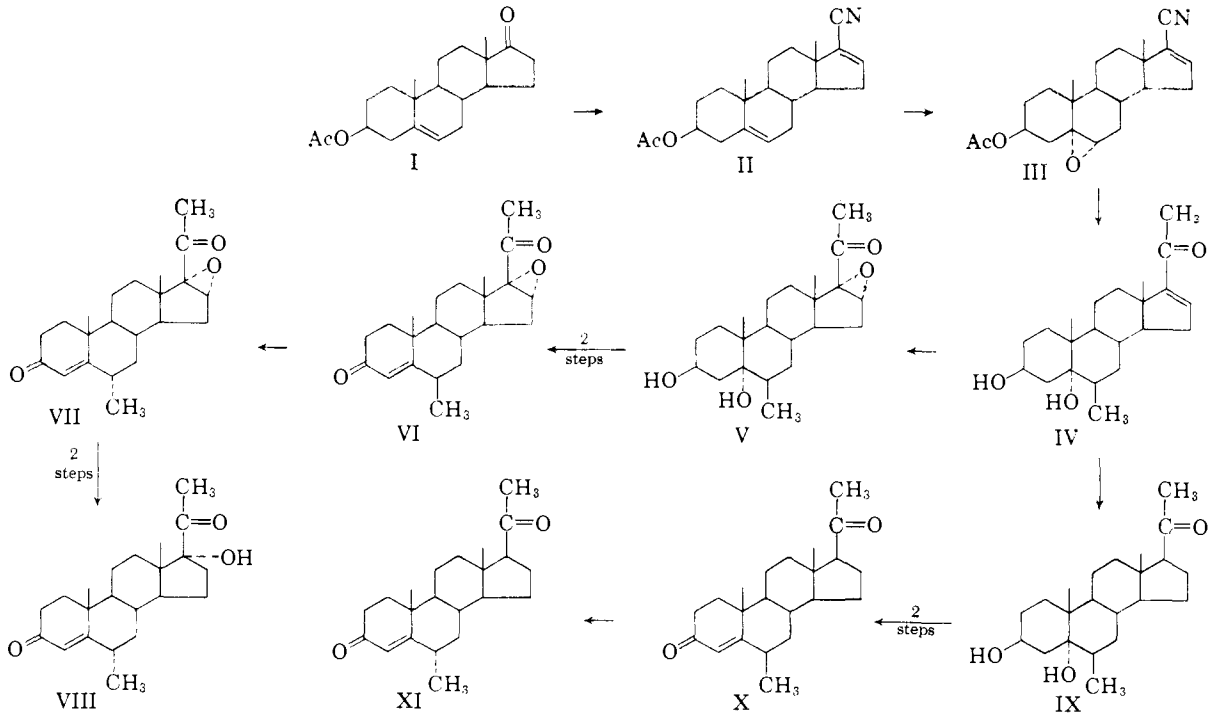
In the present work we have taken a different approach to the synthesis of 6-methyl steroids of the pregnane series. Dehydroisoandrosterone acetate was converted to a mixture of isomeric 17-cyanohydrins by a modification of Heusser's method.[2] Dehydration of this mixture afforded the known nitrile II which, upon selective peroxidation and fractional crystallization, yielded 5α,6α-epoxy-17-cyano-16-androsten-3β-ol acetate (III). Attempts to perform a two-phase reaction on III with methylmagnesium bromide in benzene or toluene were fruitless. However, in anisole the reaction proceeded smoothly to give 3β,5α-dihydroxy-6β-methyl-16-pregnen-20-one (IV) which was consecutively hydrogenated (IX), oxidized and dehydrated to obtain the known 6β-methyl- (X) and 6α-methylprogesterone (XI).[1b]

Epoxidation of IV followed by oxidation and dehydration afforded 16α,17α-epoxy-6β-methyl-4-pregnene-3,20-dione (VI). This compound was epimerized (VII) and the 17α-hydroxyl group was then introduced by opening the epoxide with hydrogen bromide. Removal of the bromine with Raney nickel yielded 17α-hydroxy-6α-methylprogesterone (VIII) whose physical constants are in good agreement with those reported by Babcock, *et al.*[1d]

(2) H. Heusser, P. Th. Herzig, A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).



Experimental

3β-Acetoxy-17-cyano-5,16-androstadiene (II).—Acetic acid (385 ml.) was added during a 40-minute period at 10° to a stirred mixture of 60 g. of dehydroisoandrosterone acetate and 360 g. of potassium cyanide in 2 l. of alcohol. The mixture was stirred for an additional hour at 10° and then for 2 hours at room temperature. After dilution with water the precipitated product was collected on a filter, washed with 3 l. of 2% AcOH and dried at room temperature. The yield of epimeric cyanohydrins, m.p. 124° with decomposition, $[\alpha]_D$ −93.3°, was essentially quantitative.

A mixture of the crude cyanohydrins (60 g.), anhydrous pyridine (440 ml.) and phosphorus oxychloride (75 ml.) was refluxed for 8 hours. The cooled solution was poured with vigorous stirring onto a mixture of ice and 2 l. of 3 *M* hydrochloric acid. After an additional 15 minutes stirring the solid was collected by filtration, washed thoroughly with dilute hydrochloric acid and then with water until neutral. The moist product was dissolved in acetone, treated with Darco and the solution concentrated to a small volume to obtain 43 g. of pure II, m.p. 208–211°, $[\alpha]_D$ −71.6°.

5α,6α-Epoxy-17-cyano-16-androsten-3β-ol Acetate (III).—A solution of 46 g. of the nitrile II and anhydrous potassium acetate (460 mg.) in dichloromethane (310 ml.) was treated with a mixture of 40% peracetic acid (37 ml.) and anhydrous potassium acetate (1.84 g.) in dichloromethane (46 ml.), keeping the temperature below 25°. The mixture was stored at room temperature for 4 hours and then washed successively with water, 5% sodium bicarbonate solution and again with water until neutral. Evaporation of the dried solution and addition of ether gave 24.1 g. of the epoxide III, m.p. 187–190°. One crystallization from dichloromethane–methanol produced 20.4 g. melting at 191–194°, $[\alpha]_D$ −64.7°.

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22, N, 3.94. Found: C, 74.43; H, 8.38; N, 3.93.

Saponification was effected by refluxing 0.5 g. of the acetate with sodium bicarbonate (0.5 g.) in 220 ml. of 90% alcohol for 1 hour. Concentration of the solution to one-third its volume and dilution with water gave 400 mg. of the carbinol, m.p. 206–208°, which, after crystallization from acetone–ether melted at 211–213°, $[\alpha]_D$ −78.5°.

3β-5α-Dihydroxy-6β-methyl-16-pregnen-20-one (IV).—Forty grams of the epoxynitrile acetate III dissolved in anisole (300 ml.) was added dropwise to a stirred, 3 *M* ether solution of methylmagnesium bromide (480 ml.). After a 12-hour heating at 60°, the cooled mixture was added during 1.5 hours to a stirred solution of 2000 ml. of acetic acid and 2000 ml. of water. The mixture was then heated on a steam-bath for 0.5 hour while 200–300 ml. of the mixed solvent distilled, after which the remaining solvent was removed by steam distillation. The cooled suspension of crystalline solids was treated with 800 ml. of 6 *M* hydrochloric acid, and the product was collected on a filter, washed well and dried. The crude IV, melting at 205–210°, weighed 37.1 g. Crystallizations from chloroform–ether and finally from methanol yielded 14.8 g. of pure IV, m.p. 253–256°, $[\alpha]_D$ +7.6°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.29; H, 9.76.

3β,5α-Dihydroxy-16α,17α-epoxy-6β-methylpregnan-20-one (V).—To a solution of 1.0 g. of IV, m.p. 250–252°, $[\alpha]_D$ +8.2°, in methanol (60 ml.) was added 35% hydrogen peroxide (3.6 ml.) and a solution of sodium hydroxide (360 mg.) dissolved in 2 ml. of water. The mixture was stored at room temperature for 24 hours and then diluted with water to recover 980 mg. of the epoxide V, m.p. 202–204°, $[\alpha]_D$ +22.2°.

Acetylation produced the corresponding 3-acetate, m.p. 210–213°, $[\alpha]_D$ +25°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.27; H, 8.81.

5α-Hydroxy-16α,17α-epoxy-6β-methylpregnan-3,20-dione.—A solution of 2.2 g. of chromic acid in acetic acid–water (9 ml. of each) was added to a stirred solution of 6.9 g. of the epoxide V in 120 ml. of acetic acid and the mixture was further stirred at 45–48° for 1.5 hours. The excess oxidant was destroyed by addition of methanol and, after 10 minutes, the solvent was removed under vacuum. Dilution of the residue with water precipitated a crystalline product which at this stage melted at 230–235°. Crystallization from dichloromethane–ether afforded 3.9 g., m.p. 248–250°, $[\alpha]_D$ +51°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 72.95; H, 8.98.

16α,17α-Epoxy-6β-methyl-4-pregnen-3,20-dione (VI).—Thionyl chloride (3.43 ml.) was added at 0° to a solution of 5α-hydroxy-16α,17α-epoxy-6β-methylpregnan-3,20-dione (4.58 g.) in pyridine (57 ml.). After 10 minutes ice-water was added to recover the crude product which melted at 176–179° and weighed 3.7 g. Crystallization from chloroform–methanol gave 3.43 g. of pure material, m.p. 188–189°, $[\alpha]_D$ +108°; λ_{max}^{MeOH} 240 mμ, ε 16,200.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.19; H, 8.58.

16α,17α-Epoxy-6α-methyl-4-pregnen-3,20-dione (VII).—One gram of the 6β-methyl isomer VI was refluxed in methanol (125 ml.) and potassium hydroxide (2.25 g.) for 35 minutes. Addition of a solution of sodium chloride, followed by filtration and drying, gave 870 mg. of crude VII, m.p. 152–155°. Crystallization from dichloromethane–methanol afforded 650 mg. of pure product, m.p. 153–156°, $[\alpha]_D$ +150°; λ_{max}^{MeOH} 240 mμ, ε 16,100.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.22; H, 8.84.

17α-Hydroxy-6α-methylprogesterone (VIII).—A solution of 500 mg. of VII in acetic acid (4.5 ml.) was treated with an excess of dry hydrogen bromide and then stored for 30 minutes at room temperature. The crude bromohydrin, recovered, by dilution with ice-water, was refluxed for 2 hours with twice its weight of Raney nickel in methanol. Filtration and removal of solvent gave a residue which, upon crystallization from aqueous acetone, weighed 305 mg. and melted at 218–220°, $[\alpha]_D$ +78°; λ_{max}^{MeOH} 240 mμ, ε 16,000. These constants are in good agreement with those previously reported.[1d]

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.77; H, 9.36. Found: C, 76.77; H, 9.51.

The 17α-acetate[1d] showed m.p. 203–205°, $[\alpha]_D$ +54°; λ_{max}^{MeOH} 240 mμ, ε 16,000.

3β,5α-Dihydroxy-6β-methylpregnan-20-one (IX).—Six grams of IV in methanol were hydrogenated using 5% palladium-on-carbon catalyst. After removal of the catalyst and evaporation of the solvent, 5.8 g. of crude product was obtained melting at 206–209°. Crystallization from methanol yielded 5.4 g. of pure diol IX, m.p. 208.5–210.5°, $[\alpha]_D$ +59.2.°

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.62; H, 10.47.

6β- and 6α-Methylprogesterone.—A solution of 1.82 g. of IX in 76 ml. of acetic acid was treated with 414 mg. of chromic acid dissolved in 15 ml. of 85% acetic acid and maintained at 45–48° for 1.5 hours. The mixture, worked up as usual, gave 1.1 g. of crude product with m.p. 225–230°. Several crystallizations from chloroform–methanol afforded 650 mg. of pure 5α-hydroxy-6β-methylpregnan-3,20-dione, m.p. 254–256°, $[\alpha]_D$ +78°.[1c] The latter product (600 mg.) was dissolved in pyridine (8 ml.) and treated at 0° with 0.5 ml. of thionyl chloride. Recovery by dilution with ice-water and crystallization from methanol gave 350 mg. of 6β-methylprogesterone, m.p. 168–169°, $[\alpha]_D$ +142°, which values agree with those of Ringold, *et al.*[1b]

Epimerization was effected by refluxing 1.0 g. of the β-isomer in 100 ml. of ethanol containing a few drops of 12 *M* hydrochloric acid for 40 minutes. After dilution with water, the crude product was collected and crystallized from methanol, affording 705 mg. of pure 6α-methylprogesterone,[1b] m.p. 118–120°, $[\alpha]_D$ +178°.

APARTADO POSTAL 1848, MEXICO D.F., MEX.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO, BOULDER, COLO.]

Bridged Polycyclic Compounds. XIII. Some Rearrangements of the Dibenzobicyclo[2.2.2]octadiene System

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An attempt to prepare dibenzobicyclo[2.2.2]octadiene-*trans*-2,3-diol by means of performic acid oxidation of dibenzobicyclo[2.2.2]octatriene has failed because of a Wagner–Meerwein rearrangement which gave dibenzobicyclo[3.2.1]octadiene-*exo*-4-*syn*-8-diol. The same rearranged diol was obtained by the treatment of dibenzobicyclo[2.2.2]octadiene-2,3-epoxide with formic acid and subsequent hydrolysis. Reaction of the epoxide with alkali led to rearrangement and ring opening with 1,2,5,6-dibenzocycloheptatriene as the product. An investigation of this rearrangement showed that 1,2,5,6-dibenzocycloheptatriene-7-carboxaldehyde was an intermediate.

A number of investigators[2] have shown that reactions which involve a bicyclo[2.2.1]heptyl cation are frequently accompanied by skeletal rearrangements. Although the bicycloöctanes have not been studied as extensively, the limited amount of available information indicates that such rearrangements also occur with bicyclo[2.2.2]octyl cations.[3] The labile nature of these intermediates presents a problem when the preparation of the bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane-*trans*-2,3-diols is attempted. The common synthetic method for *trans*-diols, namely the peracid oxidation of the corresponding olefins followed by ring opening, proceeds *via* a carbonium ion intermediate and gives bicyclo[2.2.1]heptane-2,7-diol and bicyclo[3.2.1]octane-4,8-diol instead of the expected *trans*-2,3-diols.[2jkm,3c]

For the purpose of extending some studies of elimination reactions in bicyclic systems[4] we were interested in finding a synthetic route for the two above-mentioned *trans*-glycols and the related dibenzobicyclo[2.2.2]octadiene-*trans*-2,3-diol (IX). The reaction of dibenzobicyclo[2.2.2]octatriene (I) with peroxyformic acid has not been reported in the literature. However, Vaughan[5] has shown that some highly substituted dibenzobicyclo[2.2.2]-octadienes undergo rearrangement under acid conditions to give dibenzobicyclo[3.2.1]octadiene derivatives, but that a positive charge on C_2 or C_3 does not always result in such a skeletal rearrangement. We found that treatment of dibenzobicyclo-[2.2.2]octatriene (I) with peroxyformic acid gave,

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