minutes the flask was transferred to an ice–salt-bath and kept at −10° for 6.25 hours. The reaction mixture was carefully poured into an excess of cold 5% sodium bicarbonate solution and the methylene chloride layer separated. The aqueous phase was extracted three times with methylene chloride and the combined organic extracts were then washed with water, dried over sodium sulfate and concentrated to dryness. The crystalline residue was treated overnight with 5 ml. of pyridine and 2.5 ml. of acetic anhydride. The product isolated with methylene chloride in the usual way crystallized on concentration of the dried extracts. Filtration gave 0.24 g. of 6α,9α-difluoro compound, m.p. 240–243° and raised to 255–260° after four crystallizations from acetone–hexane, $[\alpha]_D$ +113°, λ_{max}^{EtOH} 234 mμ, log ε 4.22; λ_{max}^{KBr} 5.75, 6.05 and 6.15(sh.) μ.

Anal. Calcd. for $C_{24}H_{32}F_2O_6$: C, 63.42; H, 7.10; F, 8.36. Found: C, 63.15; H, 6.96; F, 8.01.

6α,9α-Difluoro-16α-methyl-$\Delta^{1,4}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-Acetate (XVI).—A mixture of 0.163 g. of 6α,9α-difluoro-16α-methyl-Δ^4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate and 0.081 g. of selenium dioxide in 21 ml. of *t*-butyl alcohol containing 0.02 ml. of pyridine was boiled with stirring in a nitrogen atmosphere for 62 hours. Ethyl acetate (100 ml.) was then added and the solution treated with charcoal, filtered and concentrated to dryness *in vacuo*. The residue was dissolved in methylene chloride and washed three times with water. The dried organic extracts were concentrated to a small volume and the solution adsorbed on a column containing 8.4 g. of silica gel (mixed with an equal volume of Celite). Elution with mixtures of methylene chloride–acetone (12:1 and 9:1) gave 0.125 g. of product. Three recrystallizations from acetone–hexane gave the analytical sample, m.p. 260–264°, $[\alpha]_D$ +91°, λ_{max}^{EtOH} 237 mμ, log ε 4.16; λ_{max}^{KBr} 5.73, 5.80, 6.03 and 6.23 μ.

Anal. Calcd. for $C_{24}H_{30}F_2O_6 \cdot C_3H_6O$: C, 63.51; H, 7.10. Found: C, 63.90; H, 7.40.

APDO. POSTAL 2679, MEXICO, D. F.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

21-Halo-17-acyloxyprogesterones

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The preparation and progestational activity of a series of 21-halo-17α-acyloxyprogesterones and 21-halo-17α-acetoxy-6α-methylprogesterones are described. 21-Fluoro-17α-acetoxy-6α-methylprogesterone (XX) is 20 times as potent orally in the Clauberg assay as 17α-ethynyl-19-nortestosterone (Norlutin).

The successful modification of the natural steroid hormone, hydrocortisone,[1] to produce compounds of increased clinical utility has aroused the hope that similar possibilities may exist for progesterone. In this paper we shall describe the synthesis and pharmacology of 21-halo-17-acyloxyprogesterones and the corresponding 6α-methylprogesterones. The enhancement of progestational activity upon fluorination of progesterone at C-21 was first reported by Tannhauser, Pratt and Jensen[2] and was independently discovered in this Laboratory. The striking effect resulting from the introduction of the 17-acetoxy group into progesterone was reported by Junkmann.[3] The combination of these two changes on progesterone, also combined with the demonstrated utility of 6-methylation,[4] produced a series of highly active progestational agents. 21-Fluoro-17α-acetoxy-6α-methylprogesterone (XX) is the most active oral progestin of the series and is 20 times as potent in the Clauberg assay as 17α-ethynyl-19-nortestosterone (Norlutin).[5]

17α,21-Dihydroxyprogesterone (I) (Reichstein's Compound S) was converted to the corresponding 21-chloro derivative II[6] with benzenesulfonyl chloride and collidine. This, in turn, was converted to the desired 21-bromide III and 21-iodide V by the use of lithium bromide and sodium iodide, respectively. The desired 21-fluoro-17α-hydroxyprogesterone (VI) was obtained from the 21-iodide V by reaction with silver fluoride in acetonitrile. From this reaction 17,21-epoxy-4-pregnene-3,20-dione (VII)[7] was also obtained. When 21-chloro-17α-hydroxyprogesterone (II) was treated with potassium fluoride in ethanol, this epoxide, VII, became the major product. The acylation of the fluoride VI, chloride II and bromide III was accomplished by the use of the desired anhydride and *p*-toluenesulfonic acid.[8] When an attempt was made to acetylate 21-iodo-17α-hydroxyprogesterone (V) by this method the iodine was lost and 17α-acetoxyprogesterone was obtained.

(1) (a) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953); (b) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955); (c) W. S. Allen and S. Bernstein, THIS JOURNAL, **78**, 1909 (1956); (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) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff and L. H. Sarett, *ibid.*, **80**, 3160, 3161 (1958); (f) A. Bowers and H. J. Ringold, *ibid.*, **80**, 4423 (1958).

(2) P. Tannhauser, R. J. Pratt and E. V. Jensen, *ibid.*, **78**, 2658 (1956).

(3) K. Junkmann, *Arch. exptl. Path. Pharmakol.*, **223**, 244 (1954).

(4) (a) A. David, F. Hartley, D. R. Millson and V. Petrow, *J. Pharm. Pharmacol.*, **9**, 929 (1957); (b) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (c) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes and W. E. Dulin, THIS JOURNAL, **80**, 2904 (1958). This work was completed before the publication by J. C. Babcock, *et al.*, on the 6α-methyl-17α-acyloxyprogesterones appeared.

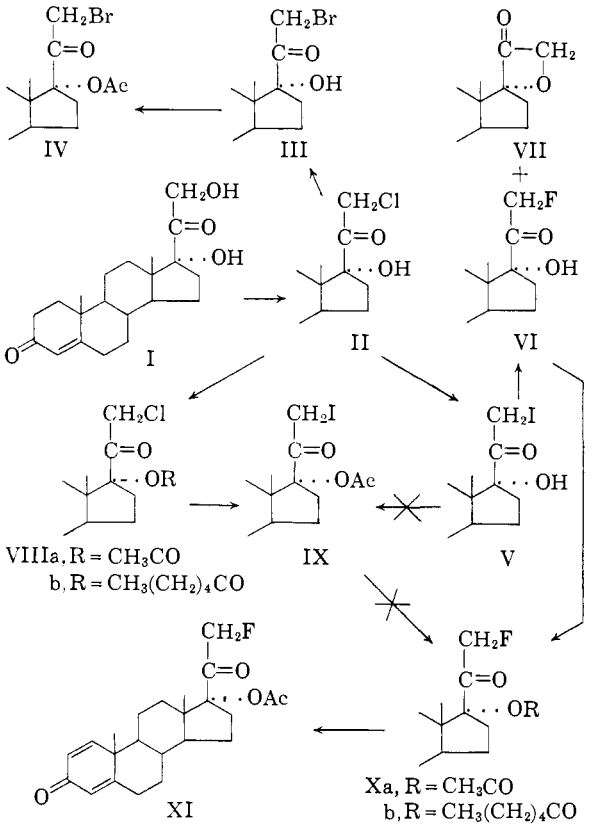
(5) (a) O. v. St. Whitelock, *Ann. N. Y. Acad. Sci.*, **71**, 479 (1958). C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 4092 (1954). Recently, publications on additional series of highly potent progestational steroids have appeared: (b) 6-dehydro-6-methyl-17α-acetoxyprogesterone: H. J. Ringold, J. P. Ruelas, E. Batres and C. Djerassi, THIS JOURNAL, **81**, 3712 (1959); R. M. Dodson and P. B. Sollman, U. S. Patent 2,891,079, June 16, 1959, (c) 6-dehydro-6-halo-17α-acetoxyprogesterones: H. J. Ringold, E. Batres, A. Bowers, J. Edwards and J. Zderic, THIS JOURNAL, **81**, 3485 (1959); (d) 9-halo-11-oxygenated-17α-acetoxyprogesterones: C. G. Bergstrom, R. T. Nicholson, R. L. Elton and R. M. Dodson, *ibid.*, **81**, 4432 (1959); (e) 21-fluoro-17α-acetoxy-6-methyl-4,6-pregnadiene-3,20-dione: P. B. Sollman, R. L. Elton and R. M. Dodson, *ibid.*, **81**, 4435 (1959).

(6) J. W. Ralls and C. G. Bergstrom, U. S. Patent 2,793,207, May 21, 1957.

(7) This type of ring closure was originally described by W. S. Allen, S. Bernstein, M. Heller and R. Littel [THIS JOURNAL, **77**, 4784 (1955)]. The details were clarified by J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo [*ibid.*, **78**, 4812 (1956)] and by R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker and J. M. Chemerda [*ibid.*, **78**, 4814 (1956)].

(8) R. B. Turner, *ibid.*, **75**, 3489 (1953).

Chart I

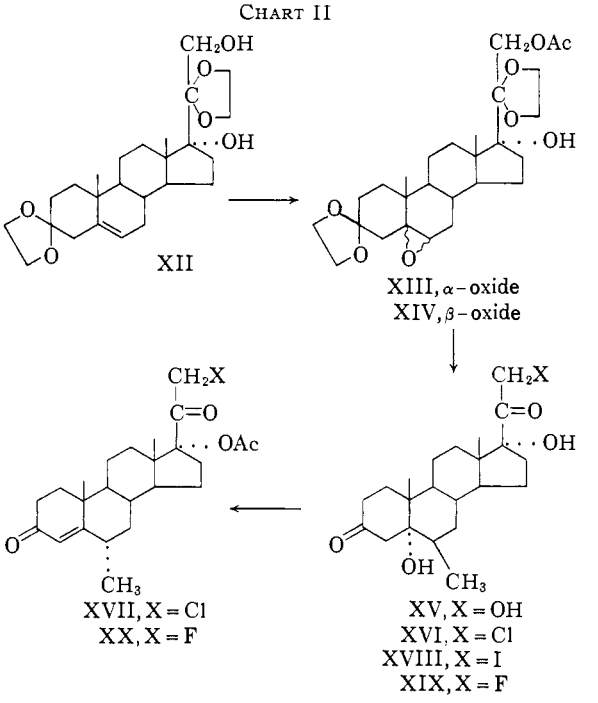


21-Iodo-17α-acetoxyprogesterone (IX) was prepared from 21-chloro-17α-acetoxyprogesterone (VIIIa) by prolonged heating with sodium iodide in acetone. Preliminary esterification of the 17α-hydroxyl group had a profound effect on the rate of displacement of the 21-chloro group with iodide ion. Thus the conversion of II to V required less than an hour while the conversion of VIIIa to IX required more than twenty-four hours under similar conditions.[9] In order to avoid the formation of the 17,21-epoxide VII, we explored the conversion of 21-iodo-17α-acetoxyprogesterone (IX) to 21-fluoro-17α-acetoxyprogesterone (Xa) using silver fluoride in acetonitrile. None of the desired 21-fluoro-17α-acetoxyprogesterone was obtained; the only product isolated was 17α-hydroxy-21-acetoxyprogesterone, and that in very small yield.

Because of the profound effect resulting from the introduction of the 1,2-double bond in hydrocortisone, this function was introduced into the most active progestin of the unmethylated series. Treatment of 21-fluoro-17α-acetoxyprogesterone (Xa) with selenous acid gave 21-fluoro-17α-acetoxy-1,4-pregnadiene-3,20-dione (XI).

The 6-methyl moiety was introduced in a straightforward manner following the general methods of Petrow.[4a] 17α,21-Dihydroxy-4-pregnene-3,20-dione (I) was converted in 40% yield to the corresponding 3,20-bisethylene ketal XII.[10] Acetylation of this ketal XII followed by epoxidation with peracetic acid produced a mixture from which 52% of the β-oxide XIV and 29% of the α-oxide XIII were isolated by chromatography.[11] The reaction of the α-oxide XIII with methylmagnesium bromide produced the expected 5α-hydroxy-6β-methyl bisethylene ketal, which, on hydrolysis with methanol–dilute sulfuric acid, gave the desired 6β-methyl-5α,17α,21-trihydroxypregnane-3,20-dione (XV). This compound, XV, could be converted to the corresponding 21-chloro derivative XVI by the use of collidine and benzenesulfonyl chloride without the loss of the 5α-hydroxyl group. Treatment of XVI with acetic anhydride and p-toluenesulfonic acid, followed by mild hydrolysis, acetylated the 17α-hydroxyl group, eliminated the 5α-hydroxyl group and epimerized the 6β-methyl group, and thus produced 21-chloro-17α-acetoxy-6α-methylprogesterone (XVII).

CHART II



In order to obtain the corresponding 21-fluoro derivative XX, 21-chloro-5α,17α-dihydroxy-6β-methylpregnane-3,20-dione (XVI) was converted to the 21-iodide XVIII with sodium iodide, and this in turn was converted by the use of silver fluoride to 21-fluoro-5α,17α-dihydroxy-6β-methylpregnane-3,20-dione (XIX). Again, treatment of XIX with acetic anhydride and p-toluenesulfonic acid, followed by mild hydrolysis, acetylated the 17α-hydroxyl group, eliminated the 5α-hydroxyl group and epimerized the 6β-methyl group, and thus produced the desired 21-fluoro-17α-acetoxy-6α-methylprogesterone (XX). The 6-methyl-3-oxo-4-ene system seems much more susceptible to oxidation to the corresponding 4,6-diene than

(9) For other examples of the difficulty of replacing an atom at C-21 in 17-acetoxypregnan-20-ones see H. J. Ringold, G. Rosenkranz and F. Sondheimer [*ibid.*, **78**, 820 (1956)] and I. Salamon and T. Reichstein [*Helv. Chim. Acta*, **30**, 1616 (1947)].

(10) R. Antonucci, S. Bernstein and R. H. Lenhard, THIS JOURNAL, **76**, 2956 (1954). A 40% yield of bisethylene ketal can be obtained from this reaction by chromatographic purification of the crude product on silica gel.

(11) This ratio of α- to β-epoxide was much less favorable than that found by A. Bowers and H. J. Ringold [*ibid.*, **80**, 3091 (1958)] using monoperphthalic acid on 17α-hydroxy-5-pregnene-3,11,20-trione 3,20-bisethylene ketal.

the unmethylated steroid X. The 21-fluoro-17α-acetoxy-6α-methylprogesterone (XX) produced in the above manner contained 8% of the corresponding 21 - fluoro - 17α - acetoxy - 6 - methyl - 4,6-pregnadiene-3,20-dione.[5e] If oxygen was not scrupulously excluded from the acetylation ands ubsequent hydrolysis, the quantity of diene produced increased.

TABLE I

Compound	Progesterone substitution 6α	17α	21	Progestational activity[a] Subcutaneous	Oral
..	H	H	H	1	0.01
...	H	H	F	2	.05
...	H	OAc	H	10	.2
Xa	H	OAc	F	10	1
VIIIa	H	OAc	Cl	2	<0.2
IV	H	OAc	Br	1	Inactive
IX	H	OAc	I	Inactive	..
Xb	H	$-OCC_5H_{11}$ (O ‖ C)	F	0.5	..
XI	Δ¹-H	OAc	F	5	..
...	CH_3	OAc	H	50	5
XX	CH_3	OAc	F	50	10
XVII	CH_3	OAc	Cl	2	..
...	17α-Ethylnyl-19-nor-testosterone (Norlutin)			0.5	0.5

[a] All values are compared to subcutaneous progesterone. Estimates of potency are obtained by comparison of the minimal effective doses of the compound and progesterone (SC) producing a +3 degree of glandular arborization. When compared orally at the +2 level the 21F-steroids are still more active than the corresponding hydrogen analogs.

The relative progestational activities of the compounds described herein, as determined by the Clauberg assay,[12] are summarized in Table I. The replacement of C-21 hydrogen by fluorine had very little effect on progestational activity when the compound was administered subcutaneously, but increased the activity when the compound was administered orally. Activity decreased regularly in going from a 21-fluoro steroid through the 21-chloro and 21-bromo to the corresponding 21-iodo compound. None of the 21-haloprogestins other than the 21-fluoro compounds had appreciable oral activity. The effect of the 6α-methyl group was not consistent. It greatly enhanced the activity of the 21-hydrogen and 21-fluoro derivatives but had no effect on the activity of 21-chloro-17α-acetoxyprogesterone. The introduction of the Δ¹-double bond into 21-fluoro-17α-acetoxyprogesterone decreased the activity. The effects of variation of the ester group at C-17 have not been fully explored, but, at least in this acute assay, the caproate was less active than the acetate.

Experimental[13]

21-Chloro-17α-hydroxy-4-pregnene-3,20-dione (II).—A suspension of 25 g. of 17α,21-dihydroxy-4-pregnene-3,20-dione in 125 ml. of benzenesulfonyl chloride and 17.5 ml. of collidine was stirred at 35–40° for 24 hours. The reaction mixture was extracted with a 2.0-l. and 1.0-l. portion of boiling petroleum ether. The insoluble sirup, on crystallization from a mixture of 1.0 l. of acetone and 0.5 l. of water, yielded 21.6 g. (81%) of product, m.p. 222–232° dec. Concentration of the mother liquors gave an additional 1.1 g. (4%) of product, m.p. 195–226° dec. The two crops were combined and crystallized from about 1.5 l. of ethyl acetate to give 17.7 g. (67%) of material, m.p. 242–247°, of sufficient purity to be used in further reactions. Further crystallization from acetone gave pure 21-chloro-17α-hydroxy-4-pregnene-3,20-dione, m.p. 247.5–249.5°.

Anal. Calcd. for $C_{21}H_{29}ClO_3$: C, 69.12; H, 8.01. Found: C, 69.19; H, 7.91.

17,21-Epoxyprogesterone (VII).—A solution of 29.06 g. of 21-chloro-17α-hydroxyprogesterone and 66 g. of potassium fluoride in 2.9 l. of ethanol (95%) was heated under reflux for 24 hours. The solvent was largely removed by distillation at reduced pressure and the residue was partitioned between water and benzene. The benzene layer was washed with water, dried over anhydrous sodium sulfate, and chromatographed on silica gel. The column was developed with benzene–ethyl acetate mixtures. The fractions eluted with 10% and with 15% ethyl acetate in benzene weighed 16.5 g., and they appeared to be an unresolved mixture of starting material and products. Elution with 40% ethyl acetate in benzene gave, after crystallization from acetone, 2.34 g. of crystals, m.p. 208–214°, whose infrared spectrum was identical with that of an authentic sample of 17α,21-dihydroxyprogesterone.

The 16.5 g. of mixture was heated under reflux with 100 g. of potassium fluoride in 1 l. of anhydrous ethanol. Small samples were removed from time to time and the steroid was precipitated with water and analyzed for chlorine by the Beilstein method. After four days a negative test had not been obtained, so 50 ml. of water was added. Seven hours later the Beilstein test was negative. The cooled reaction mixture was filtered and the filtrate was diluted with water. The first crop of crystals weighed 10.90 g., m.p. 188–194°, and the second crop weighed 2.43 g., m.p. 165–170°. Repeated crystallization of the first crop from acetone gave 2.33 g. of pure 17,21-epoxyprogesterone, m.p. 198.5–202.5°, $[\alpha]D$ +214°; λ_{max} 240 mμ, (ε 16,700); λ_{max}^{KBr} 5.51, 6.02, 6.23, 10.43 μ.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.80; H, 8.45.

Chromatography of the residue from the mother liquors on silica gel gave an additional 4.56 g. of epoxide eluted with 10 and 15% ethyl acetate in benzene. The later fractions eluted with 15% ethyl acetate in benzene contained 0.31 g. of 21-fluoro-17α-hydroxyprogesterone (VI), m.p. 223–227°. The melting point of a mixture with an authentic sample was not depressed and the infrared spectra were identical.

21-Fluoro-17α-hydroxy-4-pregnene-3,20-dione (II → V → VI).—A solution of 9.85 g. of 21-chloro-17α-hydroxy-4-pregnene-3,20-dione and 20 g. of sodium iodide in 1 l. of acetone was heated under reflux for one hour. Most of the acetone was removed by distillation at reduced pressure and the residue was partitioned between 1.0 l. of ethyl acetate and 250 ml. of dilute sodium thiosulfate solution. The ethyl acetate solution was separated and was washed with two 250-ml. portions of water. After being dried over anhydrous sodium sulfate, the ethyl acetate solution was distilled to dryness at reduced pressure. The crude crystalline 21-iodo-17α-hydroxy-4-pregnene-3,20-dione was dissolved in 1.0 l. of acetonitrile (previously dried over calcium chloride and distilled); 10 g. of silver fluoride[14] was added; and the mixture was heated under reflux for 18 hours.[15] The reaction mixture was filtered, and the filtrate was concentrated to 0.1 l. by distillation at reduced pressure. The concentrated solution was mixed with 1.0 l. of ethyl acetate and this mixture was washed with three 0.25-l. portions of distilled water. The ethyl acetate solution was dried with anhydrous sodium sulfate and was distilled to dryness at reduced pressure. The residue was chromatographed on 500 g. of silica gel. Elution with 15% ethyl acetate in benzene gave two products.

(12) C. W. Emmens, "Hormone Assay," Academic Press, Inc., New York, N. Y., 1950, p. 422.

(13) Melting points were taken on a Fisher–Johns melting point apparatus and are not corrected. Rotations were determined in chloroform at 24 ± 2°. Ultraviolet spectra were determined in methanol and infrared spectra in potassium bromide disks unless otherwise noted. The petroleum ether fraction used in crystallizations was that of b.p. 60–71° unless otherwise noted.

(14) Harshaw Chemical Co., 1945 E. 97th St., Cleveland 6, O.

(15) In subsequent runs it was felt advantageous to place the silver fluoride in the thimble of a Soxhlet extractor. Only about 40% of the solid was extractable by acetonitrile.

Crystallization of the first weight-peak from acetone gave 0.52 g. (6%) of crystals, m.p. 195–197°. Recrystallization of this material from acetone raised the m.p. to 196.5–198°, $[\alpha]D$ +215°, λ_{max} 240 mμ (ε 17,200). The infrared spectrum was identical with that of the sample of 17,21-epoxyprogesterone described above.

Crystallization of the second weight peak from methanol gave 2.55 g. (27%) of 21-fluoro-17α-hydroxy-4-pregnene-3,20-dione, m.p. 210–214°. Repeated crystallization from methanol did not improve the melting point which seemed to vary with the temperature at which the sample was placed on the melting point block and with the solvent of crystallization. Crystallization from acetone gave a mixture of prisms, m.p. 237–241°, and plates, m.p. 234–239°. Analysis of this material by paper chromatography using a petroleum ether (b.p. 86–100°)–phenyl Cellosolve system showed the sample to be homogeneous. The analytical sample had m.p. 217–223°, λ_{max} 241 mμ (ε 16,900), $[\alpha]D$ +138°.

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.39. Found: C, 72.05; H, 8.35.

21-Fluoro-17α-acetoxyprogesterone (VI → Xa).—A mixture of 500 mg. of 21-fluoro-17α-hydroxyprogesterone, 200 mg. of *p*-toluenesulfonic acid monohydrate and 2.5 ml. of acetic anhydride in 25 ml. of acetic acid was stirred under nitrogen for 16.5 hours. At the end of the reaction period all of the solid had dissolved. The reaction mixture was added slowly to 500 ml. of stirred ice-water. The resulting white precipitate weighed, after drying, 507 mg. and had a melting point of 170–205°.

Since the infrared spectrum of the crude product from a similar acetylation showed the presence of the 3-enol acetate, the crude product was hydrolyzed by treatment with 25 ml. of methanol and 0.25 ml. of concentrated hydrochloric acid for 3 hours. Precipitation of the product with water and crystallization of the product from methanol gave 292 mg. (52%) of 21-fluoro-17α-acetoxyprogesterone, m.p. 224–228°. Recrystallization of the material from methanol raised its m.p. to 227–229.5°, λ_{max} 240 mμ (ε 17,100), $[\alpha]D$ +51.5°.

Anal. Calcd. for $C_{23}H_{31}FO_4$: C, 70.74; H, 8.00. Found: C, 70.43; H, 8.23.

21-Fluoro-17α-hydroxyprogesterone 17-Caproate (VI → Xb).—A mixture of 500 mg. of 21-fluoro-17α-hydroxyprogesterone (VI), 200 mg. of *p*-toluenesulfonic acid monohydrate and 2.5 ml. of caproic anhydride in 25 ml. of caproic acid was stirred under nitrogen until all of the solid had dissolved. This required 7 days. The reaction mixture was poured into 500 ml. of ice-water, and the mixture was stirred for 2 hours. The oil–water mixture was extracted with benzene. The benzene layer was washed with 5% aqueous sodium carbonate solution, then with water, and was dried with anhydrous sodium sulfate. The oily residue, left after distillation of the benzene at reduced pressure, was dissolved in 25 ml. of methanol containing 0.25 ml. of concentrated hydrochloric acid. After the reaction mixture had stood for 2 hours at room temperature under nitrogen, it was diluted with water. The still-oily product was extracted with benzene. The benzene solution was washed free of acid, was dried over anhydrous sodium sulfate, and was distilled to dryness at reduced pressure. An oily residue weighing 640 mg. was obtained. This was purified by chromatography on silica gel. The desired product was eluted with 5% ethyl acetate in benzene, and after three crystallizations from acetone–petroleum ether, 72 mg. (11%) of pure 21-fluoro-17α-hydroxyprogesterone 17-caproate was obtained, m.p. 117–118.5°, λ_{max} 240 mμ (ε 16,550).

Anal. Calcd. for $C_{27}H_{39}FO_4$: C, 72.61; H, 8.80. Found: C, 72.27; H, 8.60.

21-Chloro-17α-acetoxyprogesterone (II → VIIIa).—21-Chloro-17α-hydroxy-4-pregnene-3,20-dione was acetylated by the method used for the preparation of the corresponding 21-fluoro compound Xa. Crystallization of the crude product from acetone gave pure material, m.p. 226–228°, $[\alpha]D$ +93.0°, λ_{max} 240.5 mμ (ε 17,300).

Anal. Calcd. for $C_{23}H_{31}ClO_4$: C, 67.88; H, 7.68; Cl, 8.71. Found: C, 67.78; H, 7.73; Cl, 8.45.

21-Chloro-17α-hydroxyprogesterone 17-Caproate (II → VIIIb).—The esterification was performed as described under the preparation of the 21-fluoro analog Xb. Since a yield of 2.92 g. of crude crystalline VIIIb, m.p. 126–133°, was obtained from 5.00 g. of II after the acid hydrolysis, the necessity for chromatography was eliminated. Crystallization of the compound from acetone–petroleum ether, followed by crystallization from benzene–petroleum ether, afforded 1.57 g. (25%) of pure 21-chloro-17α-hydroxyprogesterone 17-caproate as long needles, m.p. 135–137.5°, $[\alpha]D$ +75.5°, λ_{max} 240.5 mμ (ε 16,670).

Anal. Calcd. for $C_{27}H_{39}ClO_4$: C, 70.03; H, 8.49; Cl, 7.66. Found: C, 70.28; H, 8.10; Cl, 7.93.

21-Bromo-17α-acetoxyprogesterone (III → IV).—A solution of 1.00 g. of 21-chloro-17α-hydroxyprogesterone and 10.0 g. of freshly fused lithium bromide in 50 ml. of dry acetone was heated under reflux overnight. About half of the acetone was distilled and water was added to give 1.00 g. (89%) of crude 21-bromo-17α-hydroxyprogesterone, m.p. 199–203° dec., with previous darkening. Acetylation of this material by the method described above gave, after crystallization from methanol, plate-like crystals of 21-bromo-17α-acetoxyprogesterone, m.p. 222–225° dec., $[\alpha]D$ +97.5°, λ_{max} 240 mμ (ε 16,600).

Anal. Calcd. for $C_{23}H_{31}BrO_4$: C, 61.19; H, 6.92. Found: C, 61.10; H, 7.07.

21-Iodo-17α-acetoxyprogesterone (VIIIa → IX),—A solution of 0.86 g. of 21-chloro-17α-acetoxy-4-pregnene-3,20-dione and 1.72 g. of sodium iodide in 86 ml. of acetone was heated under reflux overnight. The reaction mixture was filtered and the filtrate was concentrated to about 20 ml. The addition of water to the hot solution caused the separation of plate-like crystals. The yield of product, m.p. 153–155° dec., was 0.80 g. Crystallization of this material from aqueous acetone gave 0.54 g., m.p. 154.5–155.5° dec. Halogen analysis showed the sample to contain 17.64% iodine and 3.18% chlorine which indicated that 39% of the original chloro compound remained. The mother liquors gave 0.43 g. of solid, m.p. 154.5–157°, which was combined with the remaining first crop material to give 0.80 g. of the mixture. This was heated under reflux with 50 ml. of acetone and 4.0 g. of sodium iodide for 5 days. A sample removed after two days gave a positive qualitative test for chlorine.[16] The product was isolated as indicated above to give 0.60 g. of crystals which had no definite m.p. but which gradually changed to a black tar between 142 and 148°. Crystallization of this material from aqueous acetone gave 0.52 g. of the desired product, m.p. 146° dec. with previous darkening, $[\alpha]D$ +125.5°, λ_{max} 240 mμ (ε 18,000).

Anal. Calcd. for $C_{23}H_{31}IO_4$: C, 55.42; H, 6.27; Cl, 0.00. Found: C, 55.75; H, 6.21; Cl, 0.00.

21-Fluoro-17α-acetoxy-1,4-pregnadiene-3,20-dione (Xa → XI).—A solution of 242 mg. of Xa and 193 mg. of hydrated selenium dioxide in 25 ml. of *t*-butyl alcohol containing 10 drops of glacial acetic acid was heated under reflux for 19 hours. The reaction mixture was partitioned between 0.25 l. of ethyl acetate and 0.10 l. of water. The ethyl acetate layer was separated and was further washed with three 0.10-l. portions of saturated aqueous sodium bicarbonate solution and with two 0.10-l. portions of water. It was dried over anhydrous sodium sulfate and then distilled at reduced pressure to a gum which was chromatographed on 20 g. of silica gel. Elution with 10% ethyl acetate in benzene gave 134 mg. of crude 21-fluoro-17α-acetoxy-1,4-pregnadiene-3,20-dione. Crystallization of this product from benzene followed by two crystallizations from acetone–petroleum ether gave 44 mg. of pure XI, m.p. 220–223°, λ_{max} 242 mμ (ε 15,300); λ_{max}^{KBr} 5.74, 5.97, 6.13, 6.22 μ.

Anal. Calcd. for $C_{23}H_{29}FO_4$: C, 71.11; H, 7.52. Found: C, 70.93; H, 7.35.

The Reaction of 21-Iodo-17α-acetoxyprogesterone (IX) with Silver Fluoride.—A solution of 200 mg. of IX in 25 ml. of acetonitrile (previously dried over calcium chloride and distilled) was placed in the pot of a soxhlet extractor while 400 mg. of silver fluoride was placed in the thimble. The apparatus was protected from light and it was left to cycle overnight. An additional 1.0 g. of silver fluoride was placed in the thimble after 6 hours. The entire reaction mixture was transfered to a separatory funnel with 0.10 l. of benzene and 0.05 l. of water. The mixture was filtered to remove a black solid. The benzene solution was separated and it was washed three times with 0.05-l. portions of water. The benzene solution was dried with calcium sulfate, and it was

(16) S. M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945, p. 42.

applied to a silica gel chromatography column. The column was developed rapidly with benzene–ethyl acetate mixtures. Elution with 10 and 15% ethyl acetate in benzene followed by crystallization from acetone–petroleum ether gave 37 mg. of starting material. Crystallization of the material eluted with 25 and 30% ethyl acetate in benzene from acetone–petroleum ether gave 9 mg. of crystals, m.p. 235–240°. The infrared spectrum of this material was identical with that of 17α-hydroxy-21-acetoxyprogesterone (Reichstein's Compound S acetate).

5,6-Epoxy-17α,21-dihydroxypregnane-3,20-dione 21-Acetate, 3,20-Bisethylene Ketal (XIII and XIV).[17]—A solution of 29.7 g. (0.0624 mole) of 17α,21-dihydroxy-5-pregnene-3,20-dione 21-acetate 3,20-bisethylene ketal[10] in a mixture of 425 ml. of chloroform and 85 ml. of methylethyldioxolane was added to a stirred, ice-cold mixture of 17.7 ml. (0.139 mole) of 15.7 *N* peracetic acid,[18] 21 ml. of methylethyldioxolane, 53 ml. of chloroform and 3.5 g. of anhydrous sodium acetate. The reaction mixture was stirred at −2° for 17 hours, and then it was shaken with two 350-ml. portions of 10% potassium carbonate solution. The organic layer was dried over anhydrous sodium sulfate and then over anhydrous potassium carbonate. The solution was concentrated, at reduced pressure, almost to dryness. The residue was crystallized from 120 ml. of methylethyldioxolane. A yield of 21.1 g. of crystals, m.p. 194–207°, consisting mainly of the β-oxide, was separated by filtration. The addition of 50 ml. of methanol to the filtrate caused the crystallization of 3.9 g. of almost pure α-oxide, m.p. 192.5–193.5°. Concentration of the filtrate to about 25 ml. gave an additional 2.5 g. of crude β-oxide, m.p. 196–205°. The addition of 20 ml. of methanol to the filtrate from the latter gave 1.3 g. of impure α-oxide, m.p. 189–191°, which on crystallization from acetone–petroleum ether gave 1.0 g. of almost pure α-oxide, m.p. 191–192.5°. The two crops of α-oxide were combined and crystallized from about 130 ml. of methanol containing 2% pyridine. A yield of 4.7 g. of pure α-oxide XIII, m.p. 193.5–194.5°, $[\alpha]_D$ −53°, was obtained.

Anal. Calcd. for $C_{27}H_{40}O_8$: C, 65.83; H, 8.18. Found: C, 65.97; H, 8.12.

Repeated crystallization of the β-oxide fractions from methylethyldioxolane and finally from 10% pyridine in acetone gave pure 5,6β-epoxy-17α,21-dihydroxypregnane-3,20-dione 21-acetate 3,20-bisethylene ketal (XIV), m.p. 210–211.5°, $[\alpha]_D$ −4.5°.

Anal. Calcd. for $C_{27}H_{40}O_8$: C, 65.83; H, 8.18. Found: C, 66.13, 65.80; H, 8.30, 8.10.

The oxide mixture could be more efficiently separated by chromatography on silica gel. Both oxides were eluted with 30% ethyl acetate in benzene. The β-oxide was eluted first, and, after crystallization, was obtained in 52% yield. The later eluates from the column gave, after crystallization, a 29% yield of the α-oxide.

21-Chloro-5α,17α-dihydroxy-6β-methylpregnane-3,20-dione (XVI).—A solution of 5.00 g. of α-oxide XIII in 90 ml. of tetrahydrofuran (freshly distilled from methylmagnesium bromide) was added to 90 ml. of 3.0 *M* methylmagnesium bromide in ethyl ether. This solution was heated under reflux for 50 hours. The excess Grignard reagent was destroyed with 1.5 l. of wet ether. The ether solution was extracted with 1.2- and 0.6-l. portions of 20% ammonium chloride solution. The combined aqueous layers were extracted with 0.50 l. of ether. The combined ether solutions were washed with two 0.20-l. portions of saturated sodium chloride solution and the ether layer was dried with anhydrous sodium sulfate. Distillation of the ether solution at reduced pressure left a crystalline residue, which, after washing with 90 ml. of ether, gave 4.18 g. of crude 5α,17α,21-trihydroxy-6β-methylpregnane-3,20-dione bisethylene ketal, m.p. 210–215°.

The crude bisethylene ketal, 2.85 g., was hydrolyzed by heating it under reflux for 10 minutes in 220 ml. of methanol containing 22 ml. of an 8.5% (v./v.) sulfuric acid–water solution. The solvents had previously been boiled to eliminate air, and a nitrogen atmosphere was maintained throughout the hydrolysis. The hydrolysis mixture was poured into 1.0 l. of saturated sodium bicarbonate solution which was then extracted with 0.50-, 0.40-, 0.30- and 0.20-l. portions of chloroform. The combined chloroform extracts were washed with 0.20 l. of saturated sodium chloride solution and then with 0.25 l. of water. The washed chloroform solution was dried with anhydrous sodium sulfate and distilled at reduced pressure to give 2.40 g. of crude 5α,17α,21-trihydroxy-6β-methylpregnane-3,20-dione (XV), m.p. 215–225°. The infrared spectrum showed a single band in the carbonyl region at 5.84 μ. There was no indication of an α,β-unsaturated ketone.

A mixture of 2.39 g. of crude triol XV, 17 ml. of freshly distilled benzenesulfonyl chloride and 1.7 ml. of γ-collidine was stirred at room temperature, under nitrogen, for 16 hours. The product was precipitated with petroleum ether and the resulting gum was crystallized by trituration with 1:3 acetone–petroleum ether. The product was washed free of benzenesulfonyl chloride with petroleum ether. After washing with water to remove collidine hydrochloride the weight of dry solid, m.p. 190–230°, was 1.4 g. Crystallization of this material from acetone gave 0.90 g. of pure 21-chloro-5α,17α-dihydroxy-6β-methylpregnane-3,20-dione, m.p. 245–247° dec.; λ_{max}^{KBr} 2.92, 5.78 and 5.90 μ. There were no strong absorption bands in the ultraviolet.

Anal. Calcd. for $C_{22}H_{33}ClO_4$: C, 66.58; H, 8.38. Found: C, 66.45; H, 8.49.

21-Chloro-17α-acetoxy-6α-methylprogesterone (XVI → XVII).—This synthesis was performed as described under the preparation of VIIIa. The yield of crude XVII from 133 mg. of XVI was 108 mg., m.p. 175–200°. Two crystallizations from acetone–petroleum ether, followed by two crystallizations from ethyl acetate gave 21 mg. of 21-chloro-17α-acetoxy-6α-methylprogesterone, m.p. 228–231°, $[\alpha]_D$ +80.2°; λ_{max} 240 mμ (ε 14,800), 289 mμ (ε 1,260).[19]

Anal. Calcd. for $C_{24}H_{33}ClO_4$: C, 68.47; H, 7.90. Found: C, 68.26; H, 7.89.

The molecular rotatory contribution of the 6-methyl group, M_D (XVII) − M_D (VIIIa), is −41°. The correspondence of this with the calculated contribution of a 6α-methyl group, ΔM_D −60°, permits the assignment of the α-configuration to the 6-methyl group in XVII. The contribution of a 6β-methyl group is approximately −185°.[20]

21-Fluoro-17α-acetoxy-6α-methylprogesterone (XX).—The conversion of the 21-chloro compound XVI to the 21-fluoro-17-acetate XX was performed as described for the preparation of Xa. Pure 21-chloro-5α,17α-dihydroxy-6β-methylpregnane-3,20-dione, 1.50 g., gave 1.8 g. of crude 21-iodide XVIII which decomposed to a black solid at 135–160°. This material had bands in the infrared spectrum at 5.82 and 5.89 μ in the carbonyl region, indicating the retention of the 5α-hydroxyl group. Conversion of this to the 21-fluoro compound gave 1.5 g. of crude product melting at 175–195° which had a strong carbonyl band at 5.82 μ. Weak absorption in the infrared spectrum at 6.06 μ indicated that a relatively small amount of the conjugated ketone had been formed.

Acetylation of the crude 21-fluoro compound XIX under the conditions described for the preparation of Xa gave 1.33 g. of crude XX, mainly as the 3-enol acetate. The major carbonyl peak in the infrared spectrum was at 5.72 μ with a very weak peak at 6.00 μ. Hydrolysis of the 3-enol acetate with methanol–hydrochloric acid under nitrogen gave 1.1 g. of crude amorphous XX. By chromatography of the crude product on silica gel there was obtained, from the fractions eluted with 10% ethyl acetate in benzene, 115 mg. of crystalline XX, m.p. 188–196°. Four crystallizations from acetone–petroleum ether gave 74 mg. of 21-fluoro-17α-

(17) We are indebted to Dr. Bjarte Löken, A.-S. Borregaard, Sarpsborg, Norway, for supplying an outline of this procedure.

(18) Becco peracetic acid 40%, Becco Chemical Division, Food Machinery and Chemical Corp., Buffalo 7, N. Y.

(19) The absorption at 289 mμ indicated the presence of 21-halo-17α-acetoxy-6-methyl-4,6-pregnadiene-3,20-dione to the extent of 4.5 and 8% in XVII and XX, respectively. 6-Methyl-$\Delta^{4,6}$-3-ones show λ_{max} 289 mμ (ε 24,600); see refs. 5b and 5e.

(20) These values for the contribution of the 6-methyl group are based on reported rotations of 6-methylprogesterone, 6-methyl-17α-hydroxyprogesterone, 6-methyltestosterone and 6-methylandrostenedione: D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957); M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *ibid.*, 4099 (1957); and ref. 4b and 4c.

acetoxy-6α-methylprogesterone, m.p. 197–200°; λ_{max} 240 mμ (ε 15,400), 289 mμ (ε 2,140).[21]

Anal. Calcd. for $C_{24}H_{33}FO_4$: C, 71.26; H, 8.22. Found: C, 71.79; H, 8.18.

(21) A purer sample of this same material (identity established by mixed m.p.'s and infrared spectra) made by an alternate procedure (to be reported later) had the following physical constants: m.p. 198–200°, $[\alpha]_D$ +40.5°; λmax. 240 mμ (ε 15,700), 290 mμ (ε 525). Found: C, 71.35; H, 8.19. The molecular rotatory contribution of the 6-methyl group, $M_D(XX) - M_D(Xa) = -37°$, establishes its α-configuration.

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CHICAGO 80, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Terpenes. XI.[1] The Total Synthesis of Maaliol

BY R. B. BATES,[2] G. BÜCHI, TERUO MATSUURA[3] AND R. R. SHAFFER

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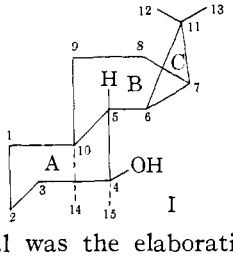
The recently proposed structure I for the tricyclic sesquiterpene alcohol maaliol has been confirmed by total synthesis. Addition of hydrobromic acid to (−)-epi-α-cyperone (IX) followed by dehydrobromination with potassium hydroxide produced the tricyclic key intermediate (XI). Wolff–Kishner reduction yielded a mixture of hydrocarbons which on oxidation with selenium dioxide gave some of the aldehyde XX. Reduction according to Wolff–Kishner followed by osmylation to the diol XXII, tosylation and hydride reduction yielded maaliol (I). A second synthesis was initiated by lithium–ammonia reduction of XI which gave an interesting array of products of which the alcohol XXV was transformed to maaliol (I) in the following manner: Acetylation followed by pyrolysis and osmium tetroxide oxidation produced, besides other products, the desired glycol XLVII. This synthesis was completed by oxidation to the acyloin and Wolff–Kishner reduction. The main synthetic paths are marked by heavy arrows.

We have recently proposed[1] structure I for the tricyclic sesquiterpene alcohol maaliol and now wish to report its synthesis.

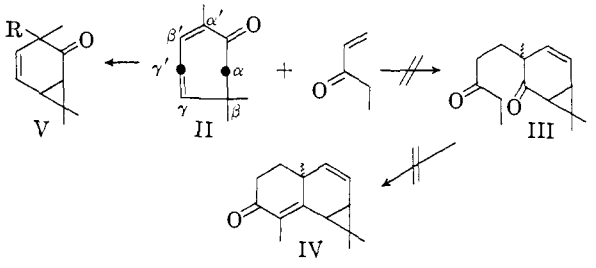


I

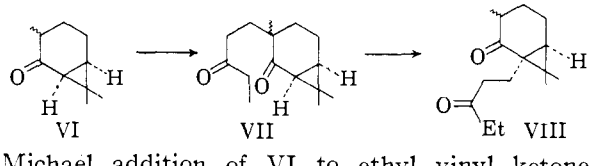
Our first goal was the elaboration of the unsaturated ketone XI for which we considered three approaches: (1) direct synthesis from the monocyclic precursor eucarvone; (2) introduction of ring A by Robinson–Mannich ring extension of the bicyclic carone; (3) ring closure of a suitable derivative of epi-α-cyperone to provide ring C. We initiated our investigations with a study of the Michael reaction of eucarvone (II) with ethyl vinyl ketone which we expected to yield the tricyclic ketone IV already containing the complete carbon skeleton of maaliol. This particular approach to the problem was patterned after the investigations of Corey and co-workers[4] who found that alkylation of eucarvone (II) leads to bicyclic (V) rather than monocyclic substitution products.

In practice the condensation of eucarvone (II) with ethyl vinyl ketone as well as with 1-chlorpentanone-3 yielded none of the desired products III and IV.

While the study of the synthesis of IV from the monocyclic eucarvone (II) was in progress we were



also investigating[5] the elaboration of its dihydroderivative XI from the bicyclic (−)-carone (VI).[6,7]



Michael addition of VI to ethyl vinyl ketone produced a bicyclic diketone (λ_{max}^{EtOH} 216 mμ, ε2790; $\nu_{max}^{CCl_4}$ 1721 (aliph. C=O), 1692 cm.$^{-1}$ (C=O conjugated with cyclopropane)) whose spectral properties are in excellent agreement with VII although the less likely alternative VIII is by no means excluded. Attempts to cyclize this diketone to a tricyclic unsaturated ketone led to recovered starting material. When efforts were made to effect cyclization at elevated temperatures, the diketone suffered retro-Michael cleavage and carone (VI) was the only isolable product.

We turn now to a discussion of the third approach which represents a convenient synthesis of the tricyclic ketone XI. It originated with (−)-epi-α-cyperone (IX) of known absolute configuration which is available in quantity by the elegant and reliable two-stage synthesis of Howe and Mc-

(1) Part X, G. Büchi, M. Schach v. Wittenau and D. M. White, THIS JOURNAL, **81**, 1968 (1959).

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(4) E. J. Corey and H. J. Burke, THIS JOURNAL, **78**, 174 (1956); E. J. Corey, H. J. Burke and W. A. Remers, *ibid.*, **78**, 180 (1956).

(5) Richard R. Shaffer, B.Sc. Thesis, M. I. T., 1958.

(6) G. Wagner, *Ber.*, **27**, 2270 (1894).

(7) A. v. Bayer, *ibid.*, **27**, 1919 (1894).