[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

THE SYNTHESIS OF SOME FLUORINE SUBSTITUTED ANTIMALARIALS

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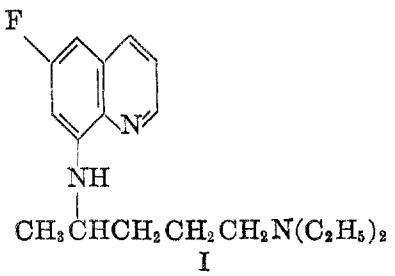
In continuation of our studies on the synthesis and action of fluorine substituted medicinals, the preparation of fluorine analogs of Plasmochin was undertaken. The fluoro-analog of Atabrine reported previously (1) was subsequently found to have antimalarial activity similar and equivalent to that of Atabrine itself.

Three synthetic routes leading to the preparation of 6-fluoro-8-aminoquinoline, the critical intermediate in the synthesis of the fluoro-analog of Plasmochin [6-fluoro-8-(4-diethylamino-1-methylbutylamino)quinoline (I)], have been investigated in detail. The first of these (Route A) involved the use of the Skraup reaction on *p*-fluoroaniline to produce 6-fluoroquinoline, which was then nitrated and the resulting 6-fluoro-8-nitroquinoline reduced to give 6-fluoro-8-aminoquinoline. An alternate synthesis (Route B) of 6-fluoroquinoline was found in the application of Roe and Hawkins' (2) modification of the Schiemann reaction to 6-aminoquinoline. The third sequence (Route C) was essentially that of Wilkinson and Finar (3) which was reported while this work was in progress. In our hands, the first of the three synthetic routes proved to be best adapted to the synthesis of sizeable amounts of 6-fluoro-8-aminoquinoline.



I

Of several procedures tried, treatment of 6-fluoro-8-aminoquinoline with Noval bromide according to a modification of the method of Elderfield, *et al.* (4) for the preparation of Plasmochin analogs (Procedure B) gave the best yields of I, although careful purification of the product was required. The compound was analyzed as the citrate.

Two other 6-fluoro-8-aminoquinoline derivatives of possible pharmaceutical interest, 6-fluoro-8-(*p*-fluorobenzenesulfonamido)quinoline and 6-fluoro-8-(7-chloro-4-quinolyl)aminoquinoline were also prepared. The three products have been submitted for pharmacological testing.

EXPERIMENTAL[1]

6-Fluoroquinoline. Route A. Skraup reaction as modified by Cohn (5). In a 2-l. 3-necked flask equipped with a glycerol-sealed stirrer and a reflux condenser were placed in order 47.0 g. of ferrous sulfate, 155.5 g. (1.4 mole) of *p*-fluoroaniline (1), 98.4 g. (0.8 mole) of nitrobenzene, and a cold solution of 85.0 g. of boric acid in 510 g. of glycerol. Then 225 ml. of concentrated sulfuric acid was added in portions with stirring and cooling. The mixture was heated cautiously to the boiling point and refluxed for 20 hours, cooled, made alkaline with concentrated sodium hydroxide, and steam-distilled. The steam-distillate was extracted thoroughly with ether. The combined ether extracts were washed with brine, dried, and the ether removed. Distillation of the residue *in vacuo* gave 202 g. (98%) of 6-fluoroquinoline, b.p. 125–126°/30 mm.

Anal. Calc'd for C_9H_6FN: N, 9.5. Found: N, 9.4, 9.6.

Route B. 6-Nitroquinoline, in 100-g. batches, was hydrogenated by the method of Haskelburg (6), and the resulting 6-aminoquinoline converted to 6-fluoroquinoline by the procedure of Roe and Hawkins (2).

6-Fluoro-8-nitroquinoline. Route A. The general procedure of Claus and Schedler (7) was employed. A mixture of 315 ml. of fuming nitric acid (*sp. gr.* 1.54) and 71.5 g. of 6-fluoroquinoline was refluxed for 100 hours. The mixture was poured onto ice and made almost neutral to litmus with ammonium hydroxide. The crude product (45.0 g.) which precipitated was filtered. Repeated recrystallization from alcohol gave 19.0 g. (25%) of 6-fluoro-8-nitroquinoline, m.p. 118.7–119.0°.

Route C. A solution of 307 g. of *p*-nitrofluorobenzene (1) in 500 ml. of acetic anhydride was hydrogenated at 30 p.s.i. in the presence of platinum oxide. When the theoretical amount of hydrogen had been absorbed, the catalyst was removed and the filtrate poured into cold water. The product was extracted with ether and the ether extracts washed, dried, and concentrated to give 261 g. (77%) of *p*-fluoroacetanilide, m.p. 149.5–150.6° after one recrystallization from water.

Nitration of *p*-fluoroacetanilide to 2-nitro-4-fluoroacetanilide was effected with either acetyl nitrate (8) or ethyl nitrate. In the acetyl nitrate method, a solution of 30.0 g. of *p*-fluoroacetanilide in 60.0 g. of glacial acetic acid and 30.0 g. of acetic anhydride was cooled to 0° and stirred vigorously while a solution of 25.0 g. of acetyl nitrate in 25.0 ml. of acetic anhydride was added at such a rate as to maintain the temperature between 0 and 5°. Stirring was continued for 20 hours, the mixture was poured onto ice, and 29.1 g. of crude 2-nitro-4-fluoroacetanilide separated as reddish oil which crystallized slowly upon standing. Recrystallization from alcohol-water gave 25.0 g. (80%) of 2-nitro-4-fluoroacetanilide, m.p. 69.5–70.5°. In the ethyl nitrate method, 29.0 g. of ethyl nitrate was added over a period of one hour to a vigorously stirred solution of 53.0 g. of *p*-fluoroacetanilide in 160 ml. of concentrated sulfuric acid at 0°. Stirring was continued for 15 additional minutes; the reaction mixture was poured onto ice and the crude material (60.0 g.) was removed. Recrystallized from alcohol-water, yield 54.1 g. (66%) of pure 2-nitro-4-fluoroacetanilide.

Hydrolysis of the acetylated product to the free amine. A mixture of 75.0 g. of 2-nitro-4-fluoroacetanilide and 190 ml. of 8 *N* hydrochloric acid was refluxed for 2 hours, made alkaline with sodium hydroxide solution, and extracted with ether. The combined ether extracts were dried over sodium hydroxide pellets, and the ether evaporated to yield 48.2 g. (83%) of 2-nitro-4-fluoroaniline melting at 93.5–94.0°.

For conversion to 6-fluoro-8-nitroquinoline, a vigorously stirred mixture of 44.0 g. of 2-nitro-4-fluoroaniline, 108 g. of glycerol, and 48.4 g. of arsenic pentoxide contained in the usual apparatus was treated with 58.6 g. of concentrated sulfuric acid at such a rate that the temperature did not exceed 130°.

The mixture was heated for 4 hours at 130–135°, and for 30 minutes at 160°. The cooled solution was diluted with water and neutralized with ammonium hydroxide to precipitate the crude 6-fluoro-8-nitroquinoline. The dry powdered solid was extracted with benzene to yield 25.2 g. (46%) of pure 6-fluoro-8-nitroquinoline, m.p. 119.2–120.0°.

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[1] All melting points are corrected, boiling points are uncorrected. Analyses by the Clark Microanalytical Laboratory, Urbana, Illinois.

6-Fluoro-8-aminoquinoline. In a 2-l. 3-necked flask equipped with a stirrer and a reflux condenser, there were placed in order 40.0 g. of 6-fluoro-8-nitroquinoline and 800 ml. of 50% aqueous acetic acid. To the mixture, under reflux, 64.0 g. of finely powdered iron was added in portions over the course of 90 minutes. Heating and stirring were continued until all of the iron was dissolved (about 3 hours), the mixture was cooled, neutralized with solid sodium hydroxide, and steam-distilled. Crude 6-fluoro-8-aminoquinoline (25.0 g., 79%), m.p. 48.0–49.5°, satisfactory for use in further synthesis, crystallized from the steam-distillate. A pure product, m.p. 50.0–50.6°, could be obtained readily by either sublimation or recrystallization from aqueous alcohol.

Anal. Calc'd for $C_9H_7FN_2$: N, 17.3. Found: N, 17.2.

6-Fluoro-8-(p-fluorobenzenesulfonamido)quinoline. A mixture of 0.81 g. of 6-fluoro-8-aminoquinoline, 0.97 g. of *p*-fluorobenzenesulfonyl chloride, and 5 ml. of dry pyridine was heated on a steam-bath for 0.5 hour and poured onto ice. The crystalline 6-fluoro-8-(*p*-fluorobenzenesulfonamido)quinoline was washed thoroughly with water and air-dried. The yield of crystalline product melting at 125.2–125.7° was 1.1 g. (68%).

Anal. Calc'd for $C_{15}H_{10}F_2N_2O_2S$: N, 8.7. Found: N, 8.5.

6-Fluoro-8-(7-chloro-4-quinolylamino)quinoline. A mixture of 1.2 g. of 6-fluoro-8-aminoquinoline monohydrochloride, 25 ml. of water, and 1.2 g. of 4,7-dichloroquinoline was heated on a steam-bath for 24 hours. A small amount of insoluble material was removed and the filtrate neutralized with aqueous ammonia. The precipitate was filtered and air-dried to give 1.3 g. (67%) of crude 6-fluoro-8-(7-chloro-4-quinolylamino)quinoline melting at 185–186°. Recrystallization from alcohol-water gave a pure product melting at 187.4–188.0°.

Anal. Calc'd for $C_{18}H_{11}ClFN_3$: N, 13.0. Found: N, 13.2.

6-Fluoro-8-(4-diethylamino-1-methylbutylamino)quinoline. A mixture of 45.0 g. of 6-fluoro-8-aminoquinoline and 40.0 g. of recrystallized Noval bromide in 50 ml. of 50% alcohol was heated continuously for 1 hour at 45–50°, for 1 hour at 60°, for 1 hour at 70°, and finally for 10 hours at reflux temperature. The mixture was treated according to the directions of Elderfield, *et al.* (4), and the isolated base was distilled in a Hickman still at 0.0008 mm. The 6-fluoro-8-(4-diethylamino-1-methylbutylamino)quinoline (20.0 g., 50%) came over steadily at bath temperature 120°. It was converted to the citrate (4), m.p. 131.0–132.2°, and analyzed in that form.

Anal. Calc'd for $C_{24}H_{34}FN_3O_7$: C, 58.4; H, 6.8; N, 8.4.
Found: C, 58.3; H, 6.7; N, 8.4.

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SUMMARY

1. A careful study has been made of three synthetic routes to 6-fluoro-8-aminoquinoline.

2. The preparation of three derivatives of 6-fluoro-8-aminoquinoline of possible pharmaceutical interest is described.

LAWRENCE, KANSAS

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

$\Delta^{5,7}$-STEROIDS. IX.[1] THE PREPARATION OF $\Delta^{4,7}$- AND $\Delta^{4,7,9}$-3-KETO-STEROIDAL HORMONES

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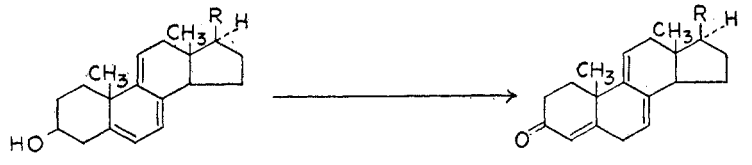
The preparation of a number of $\Delta^{5,7}$- and $\Delta^{5,7,9}$-steroidal hormones has been presented in previous papers of this series (1). These interesting compounds lend themselves to a number of well-known transformations (2). In this publication, we wish to report on one of these transformations, namely, the Oppenauer oxidation to afford $\Delta^{4,7}$- and $\Delta^{4,7,9}$-ketosteroidal hormones.

$\Delta^{5,7}$-Androstadiene-3β-ol-17-one (III) in toluene was oxidized with aluminum isopropoxide and cyclohexanone, and $\Delta^{4,7}$-androstadiene-3,17-dione (VIII) was obtained. Similarly, $\Delta^{5,7}$-pregnadiene-3β-ol-20-one (IV) gave $\Delta^{4,7}$-pregnadiene-3,20-dione (IX), and $\Delta^{5,7}$-pregnadiene-3β,21-diol-20-one-21-acetate (V) (prepared by selective acetylation of $\Delta^{5,7}$-pregnadiene-3β,21-diol-20-one) gave $\Delta^{4,7}$-pregnadiene-21-ol-3,20-dione acetate (X).

I R = C_8H_{17}
II R = C_9H_{17}
III R(H) = O
IV R = $COCH_3$
V R = $COCH_2OAc$

VI R = C_8H_{17}
VII R = C_9H_{17}
VIII R(H) = O
IX R = $COCH_3$
X R = $COCH_2OAc$

Also, $\Delta^{4,7,9}$-androstatriene-3,17-dione (XIII) and $\Delta^{4,7,9}$-pregnatriene-3,20-dione (XIV) were prepared by oxidation of $\Delta^{5,7,9}$-androstatriene-3β-ol-17-one (XI) and $\Delta^{5,7,9}$-pregnatriene-3β-ol-20-one (XII) respectively.



XI R(H) = O
XII R = $COCH_3$

XIII R(H) = O
XIV R = $COCH_3$

[1] Paper VIII. Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, **16**, preceding paper.

The structures assigned to these ketosteroids were based principally on their ultraviolet absorption spectra. The three $\Delta^{4,7}$-3-ketosteroids (VIII–X) have an absorption maximum at 237–238.5 mμ (range of three compounds). This value was in excellent agreement with the values of 238 and 239 mμ observed by us for the previously described $\Delta^{4,7}$-cholestadiene-3-one (VI) (3) and $\Delta^{4,7,22}$-ergostatriene-3-one (VII) (4) respectively. Also, the assigned structures of the $\Delta^{4,7}$-3-ketosteroids were further supported by the argument that if during the oxidation the C_7-double bond had migrated into conjugation with the α,β-unsaturated ketone known[2] compounds would have been produced. Moreover, $\Delta^{4,6}$-3-ketosteroids have an absorption maximum at 282–285 mμ (range of four compounds). In this connection we have redetermined the ultraviolet absorption spectrum of the known $\Delta^{4,6,22}$-ergostatriene-3-one (4a, c).

Both $\Delta^{4,7,9}$-3-ketosteroidal hormones (XIII, XIV) have an absorption maximum at about 242 mμ (ϵ_{242} 27,200, $\epsilon_{242.5}$ 27,200 resp.). This was in good agreement with the value of 242 mμ (ϵ 31,600) for $\Delta^{4,7,9,22}$-ergostatetraene-3-one reported by Heilbron and coworkers (4c). The location of the maximum at 242 mμ rather than at longer wavelengths, *e.g.* 282 mμ, indicates that during the oxidation *only* the C_5-double bond migrated into conjugation with the newly formed C_3-keto-group. Further substantiation of the structures assigned to XIII and XIV may be found in the magnitude of the molecular extinction coefficients. There is more or less additivity of the extinction coefficients of the two conjugated systems.[3]

The hormone assays of these $\Delta^{4,7}$-and $\Delta^{4,7,9}$-3-ketosteroidal hormones will be presented elsewhere by others.

In a future publication we plan to present a general analysis of the optical rotatory data and the infrared absorption spectra of the steroidal hormones discussed in this series.

EXPERIMENTAL

Ultraviolet absorption spectra. All spectra were determined with a Beckman quartz spectrophotometer (Model DU, mfg'd by the National Technical Laboratories, So. Pasadena, California), and were determined in commercial absolute alcohol.

Melting points. All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers (total immersion).

Optical rotations. The sample was dissolved in chloroform to make a 2-ml. solution, and the rotation was determined in a 1-dcm. semi-micro tube. The rotation was determined for two wavelengths, 5893 Å (D) and 5461 Å (Hg).

All reactions and distillations were carried out in a nitrogen atmosphere.

Dehydrocholestenone (*$\Delta^{4,7}$-Cholestadiene-3-one*) (VI).[4] 7-Dehydrocholesterol (I) (25 g.,

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[2] (a) Ruzicka and Bosshard, *Helv. Chim. Acta*, **20**, 328 (1931); $\Delta^{4,6}$-androstadiene-3,17-dione: m.p. 173°, λ_{max} 285 mμ (log ϵ = 4.7) (no solvent stated). (b) Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940); $\Delta^{4,6}$-pregnadiene-3,20-dione: m.p. 147–148°, $[\alpha]_D$ +149.5° (alc.), $\lambda_{max}^{alc.}$ 282 mμ (4.40); $\Delta^{4,6}$-pregnadiene-21-ol-3,20-dione: m.p. 115–116°, $[\alpha]_D$ +151.5° (alc.), $\lambda_{max}^{alc.}$ 83 mμ (4.53).

[3] Δ^4-3-Ketone, *e.g.*, Δ^4-androstene-3,17-dione, $\lambda_{max}^{abs.alc}$ 238.5–240 mμ, ϵ=15,800. $\Delta^{7,9}$-Diene, *e.g.*, $\Delta^{7,9}$-ergostadiene-3β-ol acetate, $\lambda_{max}^{alc.}$ 235 and 242 mμ, ϵ=13,400, 13,400 resp. [Barton and Cox, *J. Chem. Soc.*, 219 (1949)].

[4] Windaus and Kaufmann (3): m.p. 88°, λ_{max}^{ether} 231 mμ (est.)

0.065 M) in 500 ml. of toluene and 100 ml. of cyclohexanone was oxidized (*vide infra*) with with 13.2 g. (0.065 M) of aluminum isopropoxide (31.4 ml. of stock toluene solution, 1 ml. equivalent to 0.422 g. of isopropoxide). The crude product was an oil which was dissolved in acetone-methanol. Addition of water gave an oil which was separated by decantation. The procedure was repeated. Working of the oil gave a semi-solid which was also obtained by similar treatment of the decantates. The semi-solids were dissolved in acetone, and treated with water. Working of the mixture gave a semi-solid which was separated by filtration. It was dissolved in dimethylformamide and crystals were obtained by cooling the solution. They were collected and washed with methanol. Recrystallization from dilute acetone gave 6.6 g., m.p. 86–88°, λ_{max} 238 mμ, ϵ = 15,500. Working of the mother liquors and decantates gave 2.3 g., m.p. 89–89.5°.

Ergosterone ($\Delta^{4,7,22}$-*Ergostatriene-3-one*) (VII).[5] Ergosterol (II) (90 g., 0.228 M) in 2150 ml. of toluene and 430 ml. of cyclohexanone was oxidized (*vide infra*) with 47 g. (0.23 M) of aluminum isopropoxide (toluene stock solution, 1 ml. $\cong$ 0.422 g.). Recrystallization of the crude product from acetone gave 38.2 g., m.p. 133.5–135°, λ_{max} 239 mμ, ϵ = 15,100. From the mother liquors two additional fractions were obtained, 19.2 g., m.p. 131–132.5° and 5.0 g., m.p. 127–131°.

Isoergosterone[6] ($\Delta^{4,6,22}$-*ergostatriene-3-one*). Ergosterone (VII) (0.5 g.) in 3.8 ml. of 10% conc'd hydrochloric acid-glacial acetic acid was refluxed for $\frac{3}{4}$ hour. The product was worked up in carbon tetrachloride, and the crude product was recrystallized from dilute methanol and methanol, m.p. 109–112°, λ_{max} 284 mμ, ϵ = 26,400.

$\Delta^{4,7}$-*Androstadiene-3,17-dione* (VIII). A solution of 1.74 g. (0.0061 M) of $\Delta^{5,7}$-androstadiene-3β-ol-17-one (III) in 150 ml. of toluene and 25 ml. of cyclohexanone was distilled until a small amount of distillate was collected (for removal of traces of water). To the refluxing solution was added dropwise 6.2 ml. of a stock solution of aluminum isopropoxide in toluene [1 ml. $\cong$ 0.422 g., 2.61 g. (0.0128 M)]; the mixture was refluxed for 1$\frac{1}{4}$ hours, cooled, and treated with cold dilute sulfuric acid. The product was worked up in toluene, and the extract was washed with water, and steam-distilled. The product was now worked up in benzene-ether. The extract was washed with water and dried. Evaporation gave a residue which was crystallized from dilute methanol, m.p. 123–128° (with previous softening). One recrystallization from dilute acetone and two from acetone-petroleum ether[7] gave 0.43 g. of VIII, m.p. 138–141°, λ_{max} 237 mμ, ϵ = 14,700. Two more recrystallizations from acetone-petroleum ether gave 0.13 g. of VIII, m.p. 140–142°, λ_{max} 237 mμ, ϵ = 14,800, $[\alpha]_D^{29}$ +94.0°, $[\alpha]_{Hg}^{29}$ +126° (10 mg., α_D^{29} +0.47°, α_{Hg}^{29} +0.63°) α_{Hg}/α_D = 1.34. $[M]_D$ +267°.

Anal. Calc'd for $C_{19}H_{24}O_2$ (284.38): C, 80.24; H, 8.51.
Found: C, 80.01; H, 8.68.

$\Delta^{4,7,9}$-*Androstatriene-3,17-dione* (XIII). A solution of 1.00 g. (0.00352 M) of $\Delta^{5,7,9}$-androstatriene-3β-ol-17-one (XI) in 75 ml. of toluene and 15 ml. of cyclohexanone was oxidized for 1 hour with 1.43 g. (0.00704 M) (3.24 ml. of stock toluene solution) of aluminum isopropoxide. After steam-distillation, the product was worked up in ether. The ether extract was washed with water and dried. Concentration of the ether gave 0.36 g. of crude XIII, m.p. 170–185° d. Recrystallization from acetone-petroleum-ether gave 0.18 g. of pure XIII, m.p. 192.5–194.5° d., λ_{max} 235.5–236 (inflection), 242, and 248.5–249 (inflection) mμ, ϵ = 24,700, 27,200, and 22,400 respectively. $[\alpha]_D^{28}$ +468°, $[\alpha]_{Hg}^{28}$ +590° (31.7 mg., α_D^{28} +7.41°, α_{Hg}^{28} +9.35°) α_{Hg}/α_D = 1.26. $[M]_D$ +1320°.

Anal. Calc'd for $C_{19}H_{22}O_2$ (282.37): C, 80.81; H, 7.85.
Found: C, 81.12; H, 8.08.

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[5] Heilbron, *et al.*, (4c): m.p. 132°, $\lambda_{max}^{alc.}$ 230, and 320 mμ, log ϵ = 4.30, 1.61 resp.

[6] Wetter and Dimroth (4a); m.p. 105, λ_{max} 275 and 334 mμ; Heilbron, *et al.* (4c); m.p. 108, $\lambda_{max}^{alc.}$ 280 and 335 mμ, log ϵ_{280} = 4.52; Barton, Cox, and Holness, *J. Chem. Soc.*, 1771 (1949); m.p. 105°.

[7] The petroleum ether used was purified with potassium permanganate and conc'd sulfuric acid; b.p. 64–66°.

$\Delta^{4,7}$-*Pregnadiene-3,20-dione* (IX). A solution of 2.0 g. (0.0064 M) of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one (IV) in 170 ml. of toluene and 40 ml. of cyclohexanone was oxidized for 45 minutes with 2.62 g. (0.013 M) of aluminum isopropoxide (6.2 ml. of stock toluene solution). After the steam-distillation the product was worked up in ether, and the extract was washed three times with water, dried, treated with Norit, and filtered. The filtrate was concentrated with the simultaneous addition of acetone, followed by petroleum ether. This gave 0.50 g. of practically pure IX, m.p. 120–122°, λ_{max} 237.5 mμ, ϵ = 14,600. The product was recrystallized several times from acetone-petroleum ether and from dilute acetone, m.p. 119–121°, λ_{max} 237.5–238.5 mμ, ϵ = 14,100. $[\alpha]_D^{29}$ +96.9°, $[\alpha]_{Hg}^{29}$ +120°. (16.1 mg., α_D^{29} +0.78°, α_{Hg}^{29} +0.97°). α_{Hg}/α_D = 1.25. $[M]_D$ +302°.

Anal. Calc'd for $C_{21}H_{28}O_2$ (312.43): C, 80.73; H, 9.03.
Found: C, 80.67; H, 9.06.

$\Delta^{4,7,9}$-*Pregnatriene-3,20-dione* (XIV). A solution of 1.0 g. (0.0032 M) of $\Delta^{5,7,9}$-pregnatriene-3β-ol-20-one (XII) in 75 ml. of toluene and 15 ml. of cyclohexanone was oxidized for 1¼ hours with 1.31 g. (0.0065 M) of aluminum isopropoxide (3.1 ml. of stock toluene solution). After the steam-distillation, the product was worked up in ether, and the extract was washed with water, dried, treated with Norit, and filtered. The ether filtrate was concentrated with the simultaneous addition of methanol. This gave 0.31 g. of crude XIV, m.p. 153–156° (previous softening at 151°), λ_{max} 243 mμ, ϵ = 27,800. Three recrystallizations from methanol gave 0.12 g., m.p. 159.5–161°, λ_{max} 242.5 mμ, ϵ = 27,200, $[\alpha]_D^{26}$ +344°, $[\alpha]_{Hg}^{26}$ +427° (17.0 mg., α_D^{26} +2.92°, α_{Hg}^{26} +3.63°) α_{Hg}/α_D = 1.24. $[M]_D$ +1066°.

Anal. Calc'd for $C_{21}H_{26}O_2$ (310.42): C, 81.25; H, 8.44.
Found: C, 80.68; H, 8.51.

From the mother liquors there was obtained by recrystallization from methanol an additional 90 mg. of pure XIV, m.p. 159–161°, λ_{max} 242.5 mμ, ϵ = 27,400 $[\alpha]_D^{30}$ +336°, $[\alpha]_{Hg}^{30}$ +420° (16.0 mg., α_D^{30} +2.69°, α_{Hg}^{30} +3.36°) α_{Hg}/α_D = 1.25.

Anal. Found: C, 81.46; H, 8.68.

$\Delta^{5,7}$-*Pregnadiene-3β,21-diol-20-one-21-acetate* (V). *A.* A solution of 2.66 g. of $\Delta^{5,7}$-pregnadiene-3β,21-diol-20-one in 26.6 ml. of pyridine was treated in the cold with 0.88 ml. of acetic anhydride in 26.6 ml. of absolute ether. The mixture was allowed to stand at room temperature for 3 days. Cold dilute acetic acid was added, and the product was worked up in ether. The extract was washed successively with dilute acetic acid, water, sodium bicarbonate solution, and water, and was dried with magnesium sulfate, treated with Norit, and filtered through Celite. The filtrate was evaporated *in vacuo*, and the residue gave crystals from acetone-petroleum ether, wt. 1.83 g., m.p. 175–193°. Recrystallization from acetone gave pure V, wt. 0.38 g., m.p. 208–210°, λ_{max} 272, 282 and 294 mμ, ϵ = 12,030, 12,800, 7,650 resp. From the mother liquors there was obtained an additional quantity of product, wt. 0.19 g., m.p. 206–210°, λ_{max} 271.5, 282–283 and 294–294.5 mμ, ϵ = 9,100, 10,100, 5,700 resp.

B. In another run, a solution of 100 mg. of diol in 1 ml. of pyridine was treated in the cold with 1 ml. of an ether solution containing approximately 0.033 ml. of acetic anhydride. The mixture was allowed to stand at room temperature for 66 hours. The crude product, 69.9 mg., was dissolved in 10 ml. of ether-chloroform (8:1), and was put on an alumina column (7 g., pH 4.8), and was developed with 10 ml.-volumes of ether-chloroform solution successively from 7:2 to 1:8. This was followed by 10 ml. each of 50% chloroform-acetone and acetone. The crystalline fractions eluted with the ether-chloroform solutions were combined and recrystallized to constant m.p. from acetone-petroleum ether, wt. 35 mg., m.p. 209.5–211°, λ_{max} 272, 282 and 294 mμ, ϵ = 10,500, 11,000, 6,550 resp., $[\alpha]_D^{32}$ −37.6°, $[\alpha]_{Hg}^{32}$ −49.7° (14.9 mg., α_D^{32} −0.28°, α_{Hg}^{32} −0.37°) α_{Hg}/α_D = 1.32. $[M]_D$ = −140.

Anal. Calc'd for $C_{23}H_{32}O_4$ (372.49): C, 74.16; H, 8.66.
Found: C, 74.23; H, 8.95.

$\Delta^{4,7}$-*Pregnadiene-21-ol-3,20-dione acetate* (X). $\Delta^{5,7}$-Pregnadiene-3β,21-diol-20-one-21-acetate (V) (350 mg., 0.00094 M) in 30 ml. of toluene and 5 ml. of cyclohexanone was oxidized for 1¼ hours with 0.388 g. (0.0019 M) of aluminum isopropoxide (0.92 ml. of a stock toluene solution). After the steam-distillation the product was worked up in benzene, and the ex-

tract was washed with water, dried, treated with Norit, and filtered through Celite. Evaporation *in vacuo* of the filtrate gave a solid residue which was dissolved in acetone. The acetone solution was concentrated with the simultaneous addition of methanol, until a turbid solution was obtained. A few oil droplets separated and these were removed by decantation and filtration. The clear solution was again concentrated with the simultaneous addition of methanol. The mixture on cooling gave crystals, the amount of which was increased by cooling to −80°. The crystals were collected; wt. 0.1 g., m.p. 133–135.5° (with previous softening), λ_{max} 237 mμ, ϵ = 15,000. Recrystallization successively from acetone-methanol, methanol, dilute methanol, and dilute acetone gave pure X, m.p. 148.5–149.5°, λ_{max} 237 mμ, ϵ = 13,600; $[\alpha]_D^{30}$ +98.9°, $[\alpha]_{Hg}^{30}$ +125° (18.2 mg., α_D^{30} +0.90°, α_{Hg}^{30} +1.14°) α_{Hg}/α_D = 1.27. $[M]_D$ +366°.

Anal. Calc'd for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.16.
Found: C, 74.31; H, 8.40.

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SUMMARY

The preparation of $\Delta^{4,7}$-androstadiene-3,17-dione, $\Delta^{4,7}$-pregnadiene-3,20-dione, $\Delta^{4,7}$-pregnadiene-21-ol-3,20-dione, $\Delta^{4,7,9}$-androstadiene-3,17-dione, and $\Delta^{4,7,9}$-pregnatriene-3,20-dione has been described.

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