25 ml. of dilute hydrochloric acid. The ethyl acetate was removed at room temperature in an air stream and the resultant solid collected, m.p. 95–103°, depressing the melting point of VIII. The crude solid, dissolved in a solution containing 16 ml. of alcohol and 4 ml. of concd. sulfuric acid, was heated on the steam bath for 1 hr. The solution was poured into 50 ml. of ice water, held for 16 hr. at 5°, and extracted with ether. The product obtained after washing the ether with 5% sodium hydroxide, saturated salt, and evaporation of the ether weighed 160 mg. Crystallization from cyclohexane gave 130 mg., m.p. 149.5–153°. Further crystallization brought the melting point to 152.2–153.2°. $\lambda_{max}^{alc}$ 255.5, 294.5 mμ (ε 23,400, 8470); $\lambda_{inflect.}^{alc}$ 244, 261 mμ (ε 19,500, 21,500).

*Anal.* Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 65.00; H, 4.99.

*2,3-Dihydroxy-4-methoxyacetophenone.* A solution of 3.08 g. of 2,6-dimethoxyphenol in 107 ml. of glacial acetic acid with 15.8 ml. of acetic anhydride was treated with anhydrous boron trifluoride, holding the temperature below 30° until 96.5 g. of the gas had been added. The solution was then allowed to stand at room temperature for 48 hr. The reaction mixture was poured into 1 l. of ice and water and the filtered and washed boron complex was decomposed by boiling with 30 ml. of alcohol until it dissolved. On addition of 30 ml. of water and cooling, 2.98 g. (67%) of *2-hydroxy-3-acetoxy-4-methoxyacetophenone*, m.p. 121.5–126°, was obtained. From ethanol-water (3:2) colorless long thin prisms were obtained m.p. 123.4–125.0°.

*Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.96; H, 5.42.

When 1.0 g. of the above was refluxed for 1 hr. with 10 ml. of water, 10 ml. of concd. hydrochloric acid, and 20 ml. of alcohol, 0.68 g. of 2,3-dihydroxy-4-methoxyacetophenone, was obtained m.p. 130–134.5°, undepressed when mixed with a known sample (m.p. 130–132°).[12]

*Acknowledgment.* The assistance of the University Research Fund is gratefully acknowledged.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIV., AMERICAN CYANAMID CO.]

# The Synthesis of Certain C-21-Substituted Derivatives of 21-Deoxyhydrocortisone, 21-Deoxy-9α-fluorohydrocortisone, and Progesterone[1]

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The synthesis of certain modified steroidal hormones wherein the primary 21-hydroxy group or a 21-hydrogen is replaced by various nitrogen- and sulfur-containing moieties are reported.

At the time of this investigation it had already been shown that modification of the 21-hydroxymethylene grouping in the corticoid series could give structures retaining biological activity, although no case had been reported [2–11] by that time, or since, wherein such a modification has resulted in a dramatic increase in adrenocorticoid activity. $C_{21}$-Substituted derivatives of 4-pregnene-3,30-dione have also been described.[11–15] These compounds may be considered analogs of the mineralocorticoid deoxycorticosterone wherein the 21-hydroxy group is replaced, and also of progesterone wherein a 21-hydrogen is replaced.

In this paper we wish to report the synthesis of certain modified steroidal hormones wherein the primary 21-hydrogen is replaced by various nitrogen- and sulfur-containing moieties.

In our investigation, we have prepared C-21-substituted derivatives of 21-deoxyhydrocortisone,

(1) This investigation is part of a broad exploratory research program in the steroid field. For the previous publication from this laboratory on this program see H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, in press.

(2) H. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 4812 (1956) (21-fluoro-21-deoxycortisone).

(3) W. J. Leanza, J. P. Conbere, E. F. Rogers, and K. Pfister 3rd, *J. Am. Chem. Soc.*, **76**, 1691 (1954) (21-aldehydo derivatives).

(4)(a) J. Fried *et al.*, *J. Am. Chem. Soc.*, **77**, 4181 (1955) (21-deoxy-9α-fluoroprednisolone); *J. Am. Chem. Soc.*, **77**, 1068 (1955) (21-deoxy-9α-fluorohydrocortisone). (b) S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, *J. Am. Chem. Soc.*, **81**, 4956 (1959) (21-deoxytriamcinolone).

(5) L. H. Sarett, H. D. Brown, and A. R. Matzuk, U. S. Patent **2,853,486** (Sept. 23, 1958) (21-azido derivatives).

(6) P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955). (21-halo, cyano, thiocyano and acetylthio derivatives).

(7) C. Djerassi and A. L. Nussbaum, *J. Am. Chem. Soc.*, **75**, 3700 (1953) (21-acetylthio derivatives).

(8) A. L. Nussbaum, U. S. Patent **2,814,632** (Nov. 26, 1957) (21-acetylthio derivatives).

(9) B. G. Christensen, N. G. Steinberg, and R. Hirschmann, *Chem. & Ind.*, 1259 (1958) (21-diazo derivatives).

(10) 21-Amino-21-deoxy-9α-fluorohydrocortisone has recently been prepared by L. L. Smith and M. Marx of the Chemical Process Improvement Dept. of these laboratories; to be published.

(11) A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3710 (1959) (21-nitro derivatives).

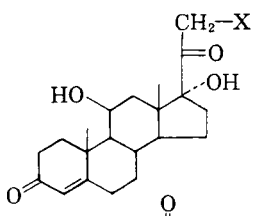
(12) P. Tannhauser, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956) (21-fluoroprogesterone).

(13)(a) S. Nakanishi, K. Morita, and E. V. Jensen, *J. Am. Chem. Soc.*, **81**, 5259 (1959) (21,21-difluoroprogesterone). (b) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5262 (1959). (c) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960). (d) 21,21,21-Trifluoroprogesterone has also been reported,[12a] however, without testing results.

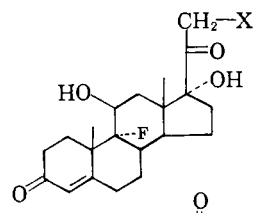
(14) R. A. Micheli and C. K. Bradsher, *J. Am. Chem. Soc.*, **77**, 4788 (1955) (21-morpholinoprogesterone).

(15) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939) (21-aldehydo derivative).

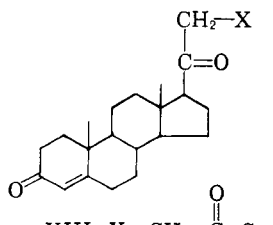
21-deoxy-9$\alpha$-fluorohydrocortisone and progesterone. These compounds were conveniently synthesized by reaction of a 21-*O*-tosylate with an appropriate nucleophile, a procedure which has been described previously by several investigators.[5,6,16] The required 21-*O*-tosylates of hydrocortisone, 9$\alpha$-fluorohydrocortisone, and deoxycorticosterone were prepared by tosylation at low temperature of the corresponding 21-ols, according to the method of Borrevang.[6] Reaction of all or certain of these three tosylates with piperidine, morpholine,[14] potassium phthalimide,[14] potassium thioacetate, sodium methylmercaptide, potassium thiocyanate, and potassium iodide then afforded the corresponding C-21-substituted analogs, usually in high yields. Although the reaction of certain 21-mesyloxy(or iodo)-17$\alpha$-hydroxy steroids with nucelophiles such as potassium fluoride and silver dihydrogen phosphate results not only in the desired displacement but also in an accompanying 17$\alpha$,21-oxide formation,[2,17] in our work we have observed no oxide formation. The free 21-mercapto derivatives were obtained in excellent yield on methanolic-methoxide treatment for fifteen minutes at room temperature of the 21-acetylthio derivatives. The various analogs are shown above (I–XVII).



I. X = $CH_3-C(=O)-S-$
II. X = HS—
III. X = $CH_3S$—
IV. X = morpholino
V. X = piperidino
VI. X = phthalimido

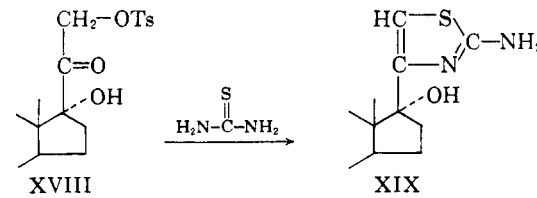


VII. X = $CH_3-C(=O)-S-$
VIII. X = H—S—
IX. X = $CH_3-S-$
X. X = NCS—
XI. X = I—
XII. X = phthalimido



XIII. X = $CH_3-C(=O)-S-$
XIV. X = H—S—
XV. X = $CH_3-S-$
XVI. X = NCS—
XVII. X = phthalimido

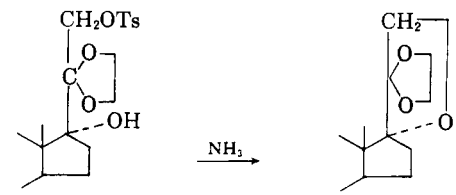
Reaction of the 21-*O*-tosylates (XVIII) with thiourea in refluxing ethanol afforded in each instance a 2-aminothiazolyl derivative (XIX).[18]



XVIII XIX

That these products were in fact 2-aminothiazolyl derivatives (XIX) was substantiated by examination of the infrared spectra which showed disappearance of the 20-carbonyl band (5.8 $\mu$) and the presence of very heavy absorption between 6.0 $\mu$ and 6.35 $\mu$ (C=N). Further support was obtained from the ultraviolet spectra where the extinction coefficient for the maximum at 241–244 m$\mu$ was approximately 20,000, a value which is substantially higher than that usually afforded by a $\Delta^4$-3-keto steroid ($\epsilon$ 16,000). The enhancement of the extinction value is consistent with the presence of a 2-aminothiazolyl chromophore (2-aminothiazole has $\lambda_{max}$ 252 m$\mu$, $\epsilon$ 7800).

Several attempts to prepare 21-unsubstituted amino derivatives *via* the reaction of 21-tosylates with ammonia or *via* the dephthaloylation of a 21-phthalimido derivative were unsuccessful.[10] Treatment of the 21-tosylate (XX) of hydrocortisone-3,20-bisethyleneketal with ammonia gave the 17$\alpha$,21-oxide (XXI).[19]



XX XXI

Most of the compounds prepared in this study were submitted for broad biological evaluation. However, no activity of significant interest was discovered.

## EXPERIMENTAL[20]

*21-Acetylthio-11$\beta$,17$\alpha$-dihydroxy-4-pregnene-3,20-dione* (I). Treatment of a solution containing 1 g. of 11$\beta$,17$\alpha$-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in 50 cc. of reagent acetone with 600 mg. of potassium thiolacetate as described below for the preparation of 21-acetylthio-9$\alpha$-fluoro-11$\beta$,17$\alpha$-dihydroxy-4-pregnene-3,20-dione (VII) gave

(16) J. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 4812 (1956).

(17) R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker, and J. M. Chemerda, *J. Am. Chem. Soc.*, **78**, 4814 (1956).

(18) The formation of thiazolyl derivatives *via* the reaction of a 21-bromo-20-keto steroid with thiourea has been reported [J. Korman, U. S. Patent **2,813,859** (Nov. 19, 1957); *Chem. Abstr.*, **52**, 5492 (1958)].

(19) W. S. Allen, S. Bernstein, M. D. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955).

733 mg. (96%) of product (I), m.p. 219–221° (gas). Two recrystallizations from acetone–petroleum ether afforded white crystals, m.p. 223–225°; $[\alpha]_D^{25}$ +151° (*c*, 1.15% in pyridine); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 19,500); $\lambda_{max}$ 2.92, 3.00, 5.80, 5.90, 6.13 μ.

*Anal.* Calcd. for $C_{23}H_{32}O_5S$: C, 65.67; H, 7.67; S, 7.63; SAc, 10.20. Found: C, 65.47; H, 7.95; S, 7.72; SAc, 10.22.

*11β,17α-Dihydroxy-21-mercapto-4-pregnene-3,20-dione* (II). Treatment of a suspension of 500 mg. of 21-acetylthio-11β,17α-dihydroxy-4-pregnene-3,20-dione (I) in 15 cc. of reagent methanol with 1.3 cc. of 1*N* methanolic sodium methoxide as described below for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-mercapto-4-pregnene-3,20-dione (VIII) afforded 296 mg. (66%) of product (II), m.p. 230° dec. Two recrystallizations from dioxane-water gave white crystals, m.p. 254° dec.; $[\alpha]_D^{25}$ +147° (*c*, 0.87% in dioxane); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 18,900); $\lambda_{max}$ 2.90, 5.85, 6.03, 6.12 μ.

*Anal.* Calcd. for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99; S, 8.46. Found: C, 66.37; H, 8.23; S, 7.97.

*11β,17α-Dihydroxy-21-methylthio-4-pregnene-3,20-dione* (III). A solution of 1 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in 50 cc. of acetone was treated with 190 mg. of sodium methylmercaptide as described below for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-methylthio-4-pregnene-3,20-dione (IX) to give 464 mg. (65%) of product (III), m.p. 217–220° (gas). Two recrystallizations from acetone–petroleum ether raised the m.p. to 223–225° (gas) $[\alpha]_D^{25}$ +141° (*c*, 1.02% in $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 241 mμ (ε 17,500); $\lambda_{max}$ 2.90, 5.85, 6.15 μ.

*Anal.* Calcd. for $C_{22}H_{32}O_4S$: C, 67.30; H, 7.96; S, 8.17. Found: C, 67.45; H, 8.19; S, 7.79.

*11β,17α-Dihydroxy-21-morpholino-4-pregnene-3,20-dione·HCl* (IV). To a suspension of 5 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in 50 cc. of reagent pyridine was added 15 cc. of morpholine, under an atmosphere of carbon dioxide, solution being complete in approximately 5 min. The stoppered solution was allowed to stand at room temperature for 18 hr. Methylene chloride (200 cc.) was added and the solution was successively washed with saturated aqueous sodium bicarbonate solution, saline, and water, dried over anhydrous magnesium sulfate, and evaporated to dryness. The residual solid was dissolved in a solution of methylene chloride-absolute alcohol. The solution was saturated with hydrogen chloride at 0° and then allowed to stand at 5–7° for 24 hr. The resulting mixture was filtered to furnish 1.29 g. (30%) of product (IV), m.p. 241–242° dec.; $[\alpha]_D^{25}$ +89° (*c*, 1.17% in pyridine); $\lambda_{max}^{CH_3OH}$ 241 mμ (ε 16,400); $\lambda_{max}$ 2.93, 3.10, 3.79, 3.91, 5.80, 5.95, 6.17 μ.

*Anal.* Calcd. for $C_{25}H_{37}NO_5·HCl$: C, 64.16; H, 8.18; Cl, 7.58; N, 2.99. Found: C, 63.84; H, 8.30; Cl, 7.75; N, 3.22.

*11β,17α-Dihydroxy-21-piperidyl-4-pregnene-3,20-dione* (V). To a suspension of 4 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in 60 cc. of reagent benzene was added 20 cc. of piperidine under an atmosphere of nitrogen. The resulting solution was allowed to stand in a stoppered flask at room temperature for 65 hr. The solution was diluted with 200 cc. of methylene chloride, washed with saturated aqueous sodium bicarbonate, then with water, dried with anhydrous magnesium sulfate, and evaporated to dryness to furnish 3.5 g. of a semisolid. Recrystallization from acetone–petroleum ether gave 2.82 g. (90%) of product (V), m.p. 150–155° (gas). Two recrystallizations from the same solvent pair afforded white crystals, m.p. 154–156° dec.; $[\alpha]_D^{25}$ +109° (*c*, 1% in methanol); $\lambda_{max}^{CH_3OH}$ 242 mμ (ε 14,000); $\lambda_{max}$ 2.93, 5.86, 6.03, 6.19 μ.

*Anal.* Calcd. for $C_{26}H_{39}NO_4$: C, 72.69; H, 9.15; N, 3.26. Found: C, 72.64; H, 9.53; N, 3.44.

*11β,17α-Dihydroxy-21-phthalimido-4-pregnene-3,20-dione* (VI). Treatment of a suspension of 1 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione[6] in *N,N*-dimethylformamide with potassium phthalimide as described below for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-phthalimido-4-pregnene-3,20-dione (XII) afforded 646 mg. (72%) of product (VI), m.p. 294–297° dec. Two recrystallizations from acetone–petroleum ether gave white crystals, m.p. 303–305° dec.; $[\alpha]_D^{25}$ +206° (*c*, 0.99% in chloroform); $\lambda_{max}^{CH_3OH}$ 220, 238 (shoulder), 293 mμ (ε 49,500; 27,000; 2,460); $\lambda_{max}$ 2.86, 5.64, 5.84, 5.98, 6.18, 7.06, 13.9 μ.

*Anal.* Calcd. for $C_{29}H_{33}NO_6$: C, 70.85; H, 6.77; N, 2.85. Found: C, 70.89; H, 6.93; N, 3.01.

*9α-Fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione.* To a suspension of 20 g. of 9α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione (9α-fluorohydrocortisone) in 200 cc. of reagent pyridine, cooled in an acetone-Dry Ice bath, was added a solution (cooled to turbidity) of 12.2 g. of *p*-toluenesulfonyl chloride in 120 cc. of methylene chloride. The suspension was stirred in the bath for 2 hr. during which period solution was completed. The solution was then allowed to stand at −20° for 17 hr. The solution was diluted with 500 cc. of ether, washed successively with water, 5% hydrochloric acid, saturated sodium bicarbonate solution, and water, dried with anhydrous magnesium sulfate, and concentrated to a small volume. The precipitated crystalline material was collected by filtration; yield 20.65 g. (74%), m.p. 110–112° (bubbling) with resolidification and remelting at 175–177°. Recrystallization from acetone-petroleum ether afforded white crystals, m.p. 181–182°; $[\alpha]_D^{25}$ +100° (*c*, 1.0% in chloroform); $\lambda_{max}^{CH_3OH}$ 228 mμ (ε 26,700); $\lambda_{max}$ 2.92, 5.75, 6.00, 8.50 μ.

*Anal.* Calcd. for $C_{28}H_{35}FO_7S$: C, 62.90; H, 6.60; F, 3.55; S, 5.99. Found: C, 62.59; H, 6.77; F, 3.26; S, 6.08.

*21-Acetylthio-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione* (VII). To a solution of 1.5 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione in 75 cc. of acetone was added 925 mg. of potassium thiolacetate. The suspension was refluxed for 2.5 hr. and then concentrated to about one-half the volume. Addition of a small amount of water caused dissolution of the solids; further addition of an equal volume of water induced crystallization. Filtration furnished 1.07 g. (87%) of product (VII), m.p. 216–218° (gas). Two recrystallizations of a sample afforded white crystals, m.p. 220–221°; $[\alpha]_D^{25}$ +150° (*c*, 1.08% in chloroform); $\lambda_{max}^{CH_3OH}$ 237 mμ (ε 20,300); $\lambda_{max}$ 2.90, 5.90, 6.03 μ.

*Anal.* Calcd. for $C_{23}H_{31}FO_5S$: C, 63.00; H, 7.13; F, 4.33; S, 7.31. Found: C, 62.81; H, 7.48; F, 4.56; S, 7.00.

*9α-Fluoro-11β,17α-dihydroxy-21-mercapto-4-pregnene-3,20-dione* (VIII). To a suspension of 633 mg. of 21-acetylthio-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (VII) in 20 cc. of reagent methanol under an atmosphere of nitrogen was added, with stirring, 1.58 cc. of 1*N* methanolic sodium methoxide, solution being complete in 30 seconds. After stirring for 10 min. the solution was acidified with 0.2 cc. of glacial acetic acid. The crystalline material that separated was collected and washed several times with water and then with ice cold methanol to furnish 411 mg. (72%) of product, m.p. 238–241° (gas). Two recrystallizations from acetone-petroleum ether gave white crystals, m.p. 251–253° (gas); $[\alpha]_D^{25}$ +85.1° (*c*, 1.01% in dioxane); $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 17,000); $\lambda_{max}$ 2.90, 3.02, 5.90, 6.06 μ.

*Anal.* Calcd. for $C_{21}H_{29}FO_4S$: C, 63.61; H, 7.37; F, 4.80; S, 8.09. Found: C, 63.41; H, 7.73; F, 4.60; S, 7.75.

*9α-Fluoro-11β,17α-dihydroxy-21-methylthio-4-pregnene-3,20-dione* (IX). To a solution of 1 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione in 50 cc. of acetone was added 200 mg. of sodium methylmercaptide. The mixture was stirred under an atmosphere of nitrogen

(20) Melting points were determined in a capillary tube and are uncorrected. All infrared spectra were determined in potassium bromide discs on a Perkin-Elmer spectrophotometer (model 21). Ultraviolet spectra were determined on a Cary recording spectrophotometer. The petroleum ether used was that fraction boiling at 60–70° unless otherwise specified. All concentrations were carried out under reduced pressure on the steam bath.

at room temperature for 4 hr. After acidification with acetic acid, a small amount of water was added and the resulting solution was concentrated to a small volume and chilled. The resulting mixture was filtered to give 656 mg. (85%) of buff-colored solid in two crops, m.p. 215–218°. A sample was recrystallized several times from acetone–petroleum ether to give white crystals, m.p. 217–219°; $[\alpha]_D^{25}$ +127° (*c*, 1% in chloroform); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 17,600); $\lambda_{max}$ 2.86, 5.90, 6.04 μ.

*Anal.* Calcd. for $C_{22}H_{31}FO_4S$: C, 64.36; H, 7.61; F, 4.63; S, 7.81. Found: C, 64.30; H, 7.68; F, 4.97; S, 7.68.

*9α-Fluoro-11β,17α-dihydroxy-21-thiocyano-4-pregnene-3,20-dione* (X). A solution of 2 g. of 9α-fluoro-11β,17α-dihydroxy-21-toxyloxy-4-pregnene-3,20-dione and 2 g. of potassium thiocyanate (dried by evaporation with 50 cc. of benzene) in 160 cc. of acetone was refluxed for 3.5 hr. The resulting mixture was concentrated to near dryness, water was added to induce crystallization, and the solid was collected by filtration to give 1.45 g. (92%) of product (X), m.p. 229–230°. Recrystallization of a sample from acetone–petroleum ether afforded white crystals, m.p. 233–235°; $[\alpha]_D^{25}$ +129° (*c*, 1.07% in methanol); $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 18,100); $\lambda_{max}$ 2.95, 4.64, 5.84, 6.05, 9.63 μ.

*Anal.* Calcd. for $C_{22}H_{28}FNO_4S$: C, 62.69; H, 6.70; F, 4.51; N, 3.33; S, 7.61. Found: C, 63.57; H, 6.88; F, 4.86; N, 3.00; S, 7.59.

*9α-Fluoro-11β,17α-dihydroxy-21-iodo-4-pregnene-3,20-dione* (XI). To a solution of 3 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione in 25 cc. of acetone was added a solution of 2.88 g. of sodium iodide in 25 cc. of acetone. After a few minutes sodium tosylate began to separate. The mixture was refluxed for 15 min., most of the acetone was distilled off, and the mixture was cooled to room temperature. On the addition of 10 cc. of 0.1*N* sodium thiosulfate and a small amount of water, a solid began to separate. The cooled solution was filtered to give 1.92 g. (70%) of product (XI), m.p. 156–158° dec. Recrystallization of a sample from acetone–petroleum ether afforded white crystals, m.p. 158° dec.; $[\alpha]_D^{25}$ +138° (*c*, 1.09% in methanol); $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 18,400); $\lambda_{max}$ 2.98, 5.85, 6.05, 6.12 μ.

*Anal.* Calcd. for $C_{21}H_{28}FIO_4$: C, 51.44; H, 5.76; F, 3.88; I, 25.88. Found: C, 51.39; H, 6.10; F, 3.54; I, 25.52.

*9α-Fluoro-11β,17α-dihydroxy-21-phthalimido-4-pregnene-3,20-dione* (XII). A suspension of 2.82 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione and 1.08 g. of potassium phthalimide in 70 cc. of *N,N*-dimethylformamide was kept in a water bath at 85–88° for 50 min., solution being complete in 5 min. The cooled solution was diluted with 200 cc. of methylene chloride and washed twice with saturated sodium bicarbonate solution and twice with water, after which a solid began to separate. The cooled mixture was filtered to furnish 1.2 g. (45%) of white crystals, m.p. 311° dec. A sample was recrystallized from acetone to give white crystals, m.p. 315° dec.; $[\alpha]_D^{25}$ +225° (*c*, 1.04% in chloroform); $\lambda_{max}^{CH_3OH}$ 220, 238 (shoulder), 293 mμ (ε 49,900; 29,000; 2,040); $\lambda_{max}$ 2.87, 5.65, 5.84, 5.97, 7.06, 13.9 μ.

*Anal.* Calcd. for $C_{29}H_{32}FNO_6$: C, 68.35; H, 6.33; F, 3.33; N, 2.75. Found: C, 68.21; H, 6.54; F, 3.66; N, 2.92.

*21-Tosyloxy-4-pregnene-3,20-dione.* Treatment of 25 g. of 21-hydroxy-4-pregnene-3,20-dione (deoxycorticosterone) in 250 cc. of reagent pyridine with a solution of 15.9 g. of *p*-toluenesulfonyl chloride in 150 cc. of methylene chloride as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione gave 21.2 g. of crude product, m.p. 157–160° dec., which by analysis was a mixture of 21-chloride and 21-tosylate.[7, 21] Relatively pure tosylate, prepared by the reaction of 21-diazoprogesterone with *p*-toluenesulfonic acid, is reported to melt at 170–171°.[22]

*21-Mercapto-4-pregnene-3,20-dione* (XIV). A suspension of 312 mg. of 21-acetylthio-4-pregnene-3,20-dione[7] (XIII) in 10 cc. of methanol was treated with 0.84 cc. of 1*N* methanolic sodium methoxide, as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-mercapto-4-pregnene-3,20-dione (VIII), to furnish 224 mg. (81%) of product (XIV), m.p. 185–188°. Three recrystallizations from acetone-petroleum ether gave white crystals, m.p. 188–190°; $[\alpha]_D^{25}$ +206° (*c*, 2.11% in chloroform); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 16,600); $\lambda_{max}$ 3.0, 5.85, 6.00, 6.16 μ.

*Anal.* Calcd. for $C_{21}H_{30}O_2S$: C, 72.79; H, 8.72; S, 9.25. Found: C, 72.54; H, 8.85; S, 8.97.

*21-Methylthio-4-pregnene-3,20-dione* (XV). Treatment of a suspension of 1 g. of 21-tosyloxy-4-pregnene-3,20-dione in 100 cc. of acetone with 220 mg. of sodium methylmercaptide, as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-methylthio-4-pregnene-3,20-dione (IX), furnished 470 mg. (63%) of product (XV), m.p. 129–135°. Four recrystallizations from acetone–petroleum ether gave white crystals, m.p. 136–138°; $[\alpha]_D^{25}$ +204° (*c*, 2.1% in chloroform); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 17,000); $\lambda_{max}$ 5.87, 5.97, 6.13 μ.

*Anal.* Calcd. for $C_{22}H_{32}O_2S$: C, 73.29; H, 8.95; S, 8.89. Found: C, 73.43; H, 9.11; S, 8.39.

*21-Thiocyano-4-pregnene-3,20-dione* (XVI). Treatment of 2 g. of 21-tosyloxy-4-pregnene-3,20-dione in 160 cc. of acetone with 2 g. of potassium thiocyanate, as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-thiocyano-4-pregnene-3,20-dione (X), gave 1.1 g. (72%) of product (XVI), m.p. 156–159°. Three recrystallizations from acetone-petroleum ether furnished white crystals, m.p. 168–170°; $[\alpha]_D^{25}$ +182° (*c*, 1% in chloroform); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 17,500); $\lambda_{max}$ 4.65, 5.82, 5.97, 6.18 μ.

*Anal.* Calcd. for $C_{22}H_{29}NO_2S$: C, 71.13; H, 7.87; N, 3.77; S, 8.63. Found: C, 70.74; H, 7.96; N, 3.95; S, 8.38.

*21-Phthalimido-4-pregnene-3,20-dione* (XVII). A suspension of 2.74 g. of 21-tosyloxy-4-pregnene-3,20-dione and 1.51 g. of potassium phthalimide in 75 cc. of *N,N*-dimethylformamide was treated as described above for the preparation of 9α-fluoro-11β,17α-dihydroxy-21-phthalimido-4-pregnene-3,20-dione (XII) to furnish 1.64 g. (63%) of product (XVII) in two crops, m.p. 215–220°. Three recrystallizations from acetone-petroleum ether afforded white crystals, m.p. 227–230°; $[\alpha]_D^{25}$ +225° (*c*, 1.59% in chloroform); $\lambda_{max}^{CH_3OH}$ 219, 236 (shoulder), 293 mμ (ε 54,500; 28,500; 2,230); $\lambda_{max}$ 5.60, 5.77, 5.95, 6.15, 13.35 μ.

*Anal.* Calcd. for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N, 3.05. Found: 75.40; H, 7.41; N, 3.29.

*17β-(2-Amino-4-thiazolyl)-4-androsten-3-one p-toluenesulfonate* (*see* XIX). A solution of 3 g. of 21-tosyloxy-4-pregnene-3,20-dione and 565 mg. of thiourea in 60 cc. of absolute alcohol was refluxed on the steam bath for 2.5 hr. After concentration to a small volume, the resulting mixture was cooled and filtered to furnish 1.94 g. (58%) of product, m.p. 265–267° dec. Recrystallization of a sample from absolute alcohol gave white crystals, m.p. 268–270° dec.; $[\alpha]_D^{25}$ +42° (*c*, 1% in methanol); $\lambda_{max}^{CH_3OH}$ 222, 227 (shoulder), 242 mμ (ε 22,800; 21,600; 20,900); $\lambda_{max}$ 5.96, 6.20, 6.34, 8.35, 8.90, 9.65, 9.88, 14.65 μ.

*Anal.* Calcd. for $C_{29}H_{38}N_2O_4S_2$: C, 64.17; H, 7.06; N, 5.16; S, 11.83. Found: C, 64.47; H, 7.28; N, 5.38; S, 11.37.

*17β-(2-Amino-4-thiazolyl)-11β,17α-dihydroxy-4-androsten-3-one p-toluenesulfonate* (*see* XIX). A solution of 4.1 g. of 11β,17α-dihydroxy-21-tosyloxy-4-pregnene-3,20-dione and 625 mg. of thiourea in 80 cc. of absolute alcohol was treated as described directly above for the preparation of 17β-(2-amino-4-thiazolyl)-4-androsten-3-one *p*-toluenesulfonate to give 1.48 g. (35%) of product, m.p. 207–208° dec. Recrystallization of a sample from absolute alcohol afforded white crystals, m.p. 212–213°; $[\alpha]_D^{25}$ +50.3° (*c*, 0.219% in dimethylformamide); $\lambda_{max}^{CH_3OH}$ 222, 227 (shoulder), 242 mμ (ε 19,000; 18,100; 18,700); $\lambda_{max}$ 2.95, 3.21, 6.01, 6.24, 6.32, 8.5, 8.9, 9.65, 9.88, 12.25, 14.65 μ.

(21) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

(22) T. Reichstein and W. Schindler, *Helv. Chim. Acta*, **23**, 669 (1940).

*Anal.* Calcd. for $C_{29}H_{38}N_2O_6S_2$: C, 60.60; H, 6.66; N, 4.87; S, 11.15. Found: C, 60.92; H, 7.19; N, 4.40; S, 11.19.

*17β-(2-Amino-4-thiazolyl)-9α-fluoro-11β,17α-dihydroxy-4-androsten-3-one p-toluenesulfonate* (*see* XIX). A solution of 3 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-androsten-3-one and 468 mg. of thiourea in 60 cc. of absolute alcohol was treated as described above for the preparation of 17β-(2-amino-4-thiazolyl)-4-androsten-3-one *p*-toluenesulfonate to give 1.14 g. (34%) of product, m.p. 214–216° dec.

In another experiment using crude 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-androsten-3-one there was obtained 2.7 g. (15%) of product, m.p. 218° dec.; $[\alpha]_D^{25}$ +38.2° (*c*, 1.05%, dimethylformamide); $\lambda_{max}^{CH_3OH}$ 222, 227 (shoulder), 242 mμ; (ε 21,000; 20,700; 19,800); $\lambda_{max}$ 2.95, 3.16, 5.99, 6.20, 6.28, 8.50, 8.90, 9.64, 9.87, 12.25, 14.70 μ.

*Anal.* Calcd. for $C_{29}H_{37}FN_2O_6S_2$: C, 58.76; H, 6.29; F, 3.21; N, 4.73; S, 10.82. Found: C, 59.44; H, 6.66; F, 3.21; N, 5.10; S, 10.56.

*17α,21-Epoxy-3,20-bisethylenedioxy-11β-hydroxy-5-pregnene* (XXI). A suspension of 500 mg. of 11β,17α-dihydroxy-3,20-bisethylenedioxy-21-tosyloxy-5-pregnene (XX)[19] in 50 cc. of methanol saturated with ammonia was kept in a steel bomb at 90–95° for 18 hr. Evaporation of the solution afforded a semi-solid. Recrystallization from acetone–petroleum ether afforded 284 mg. (79%) of crystalline material, m.p. 236–238°. Several recrystallizations from acetone gave white crystals, m.p. 253–255°; $[\alpha]_D^{25}$ 0° (chloroform), $\nu_{max}$ 3450, 1102, and 1055 cm.$^{-1}$ Reported[19] values are m.p. 252–255°; $[\alpha]_D^{25}$ 0°; $\nu_{max}$ 3500, 1102, and 1055 cm.$^{-1}$

*Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.18; H, 8.52.

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[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, KYÔTO UNIVERSITY AND FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO]

# The Preparation of Synthetic Estrogens. IX. 3,3′-Disubstituted Derivatives of Hexestrol[1]

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3,3′-Dihalohexestryl dimethyl ethers were prepared from the corresponding *m*-halo-*p*-methoxypropiophenones through reduction to the carbinol, bromination and the subsequent condensation of the Wurtz type. 3,3′-Difluoro- and 3,3′-dichlorohexestryl dimethyl ethers were demethylated smoothly by hydriodic acid, but similar treatment of 3,3′-dibromohexestryl dimethyl ether resulted in dehalogenation to give hexestrol. 3,3′-Dihalogenated butestrols were synthesized similarly. The Friedel-Crafts reaction of hexestryl dimethyl ether with various acids chlorides furnished the corresponding 3,3′-diacylhexestryl dimethyl ethers which were reduced to the respective 3,3′-dialkylhexestrols. Certain other derivatives of nuclear substituted hexestrols are described.

This paper comprises the preparation of heretofore unknown 3,3′-dihalohexestrols and -butestrols, which are of interest in their relation to 16α-chloro- and 16α-iodoestrone methyl ether, compounds reported[2] to be potent blood lipid-shifting agents of low estrogenic potency and thus of potential value in the treatment of atherosclerosis.

These halohexestrols and butestrols were synthesized according to the procedure of Bernstein and Wallis[3] as modified by Sisido and Nozaki,[4] which was summarized in the accompanying flow sheet. Treatment of 3,3′-dibromohexestryl dimethyl ether (IVc) with hydriodic acid gave a bromine-free diphenol which was identified as hexestrol. Apparently, the bromine atoms in the positions *ortho* to the methoxy groups are eliminated by the reducing action of hydriodic acid. Attempted demethylation of the dibromo ether (IVc) with hydrobromic acid yielded a reaction product from which no analytically pure compound could be isolated.[5] The action of a Grignard reagent or of pyridine hydrochloride also failed to afford any demethylation product. The 3,3′-dihalohexestrols and -butestrols are listed in Table I.

Other classes of hexestrol derivatives herein reported are 3,3′-dialkylhexestrols and related compounds. Though Buu-Hoï, Hoán, and Xuong[8] have reported the monoacylation of hexestryl dimethyl ether, the diacylated products have not

(1) For the previous paper in this series see K. Sisido, K. Okano, M. Sindô, and H. Nozaki, *J. Am. Chem. Soc.*, 79, 3591 (1957).

(2) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, 80, 1769 (1958). For the preparation of 3-fluoro-3′-hydroxyhexestrol see R. J. Pratt and E. V. Jensen, *J. Am. Chem. Soc.*, 78, 4430 (1956).

(3) S. Bernstein and E. S. Wallis, *J. Am. Chem. Soc.*, 62, 2871 (1940).

(4)(a) K. Sisido and H. Nozaki, *J. Am. Chem. Soc.*, 70, 778 (1948). (b) K. Sisido, H. Nozaki, and H. Kuyama, *J. Org. Chem.*, 14, 1124 (1949). (c) Ng. Ph. Buu-Hoï and Ng. Hoán, *J. Org. Chem.*, 14, 1023 (1949). (d) For the mechanism of the dehalogenation condensation in the presence of iron powder in water-suspension see K. Sisido, Y. Udô, and H. Nozaki, *J. Am. Chem. Soc.*, 82, 434 (1960).

(5) For examples of shift and partial elimination of bromine atoms in the demethylation of bromo ethers with hydrobromic acid see T. Tomita and T. Kugô, *J. Pharm. Soc. Japan*, 75, 1354 (1955); T. Tomita, Y. Kondo, and S. Tanaka, *J. Pharm. Soc. Japan*, 76, 1119 (1956).