g. of Celite[12] with a ternary system consisting of 1 part water, 5 parts dioxane, and 4 parts cyclohexane. The fraction collected from 2.3–3.9 hold-back volumes (HBV) (maximum product at 3.3) (1 HBV = 485 ml.) was evaporated to afford 604 mg. of crude IIa. Two crystallizations from acetone gave pure IIa, m.p. 262–270° with previous softening and browning and with decomposition at 271°; $\lambda_{max}^{methanol}$ 237 mμ (ε 17,400); ν_{max}^{KBr} 3510, 3400, 3250, 1754, 1657, 1640–1615 (inflection) cm.$^{-1}$; $[\alpha]_D^{25}$ +157° (methanol); positive Blue Tetrazolium test.

Anal. Calcd. for $C_{19}H_{25}O_4F$ (336.39): C, 67.83; H, 7.49; F, 5.65. Found: C, 67.64; H, 7.65; F, 5.86.

16α-Acetoxy-9α-fluoro-11β,17α,20-trihydroxy-4-pregnen-3-one (IV). A solution of 350 mg. of 16α-acetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (III) in 50 ml. of methanol was cooled to 0° and treated with 47 mg. of sodium borohydride. After remaining at 0° for 1 hr., the solution was acidified with 0.2 ml. of glacial acetic acid and evaporated. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution and water. The dried extract was evaporated and the residue crystallized from acetone-petroleum ether to afford 254 mg. of crude IV, m.p. 215–219.5° with previous softening. Two additional crystallizations from the same solvent pair gave 228 mg., m.p. 214.5–217.5° with previous softening; $\lambda_{max}^{methanol}$ 240 mμ (ε 11,000); ν_{max}^{KBr} 3430, 1725, 1666, 1625, 1277, and 1253 cm.$^{-1}$; $[\alpha]_D^{25}$ −19° (acetone).

Anal. Calcd. for $C_{23}H_{33}O_6F$ (424.49): C, 65.07; H, 7.84; F, 4.48. Found: C, 64.99; H, 8.17; F, 4.19.

This material was used as such in the subsequent side chain degradation.

16α-Acetoxy-9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (IIb). A. Forty milligrams of IIa in 2 ml. of pyridine was treated with 1 ml. of acetic anhydride, and the mixture was allowed to stand at room temperature overnight. The crude acetate was subjected to partition chromatography on 31 g. of Celite[12] with the system four parts petroleum ether (b.p. 90–100°), three parts ethyl acetate, four parts methanol, and two parts water. The fraction collected from 3.5–5.5 hold-back volumes (maximum product at 4.7) (1 HBV = 38 ml.) was evaporated, and the residue was crystallized from acetone-petroleum ether (b.p. 35–60°) to afford pure IIb, m.p. 248–250°. Its infrared spectrum was identical with that obtained in preparation B.

B. A solution of 380 mg. of impure 16α-acetoxy-9α-fluoro-11β,17α,20-trihydroxy-4-pregnen-3-one (IV) in 20 ml. of methanol was treated with 7.6 ml. of an aqueous solution of sodium periodate (0.1*M*). After standing at room temperature for 19 hr., the solution was poured into ice water, and the resultant precipitate was filtered and washed with water to afford 178 mg. of crude product, m.p. 227.5–236° with previous softening. Three crystallizations from acetone-petroleum ether (b.p. 60–70°) gave 129 mg. of material having a constant melting point (233–239°). Paper strip chromatography indicated approximately 75% of pure IIb together with 25% of a more polar contaminant. A 110 mg. portion of the above 129 mg. was subjected to partition chromatography on Celite[12] using a solvent system consisting of three parts of petroleum ether (b.p. 90–100°), two parts of ethyl acetate, three parts of methanol and two parts of water. The eluate from the second hold-back volume (1 HBV = 320 ml.) was evaporated and the residue crystallized from acetone-petroleum ether to afford 78 mg. of pure IIb, m.p. 246.5–249° with previous softening. One additional crystallization did not alter the melting point; $\lambda_{max}^{methanol}$ 238 mμ (ε 16,300); ν_{max}^{KBr} 3510, 1770, 1755, 1662, 1630, 1245, and 1220 cm.$^{-1}$; $[\alpha]_D^{25}$ +121° (chloroform). Paper strip chromatography indicated an homogeneous compound.

Anal. Calcd. for $C_{21}H_{27}O_5F$ (378.43): C, 66.73; H, 7.19; F, 5.02. Found: C, 67.16; H, 7.54; F, 4.75.

Acknowledgment. We wish to thank Louis M. Brancone and associates for the analyses, William Fulmor and associates for the infrared and ultraviolet absorption spectra and optical rotation data, and Robert H. Blank for the paper chromatographic analyses.

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(12) The adsorbent was specially treated Celite 545 which was slurried in 6*N* hydrochloric acid and allowed to stand overnight. It was then filtered and was washed with water, followed by a mixture of methanol and ethyl acetate. Finally, it was dried at room temperature. Celite is the trademark of Johns-Manville Company for diatomaceous silica products.

Steroidal Hormone Relatives. VIII. A Synthetic Approach to 6-Aza-equilenin[1,2]

J. H. BURCKHALTER AND JOHN A. DURDEN, JR.

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Estrogens are carcinogenic to experimental animals which have an inherited sensitivity to the development of mammary carcinoma, and many clinicians will not employ them in the treatment of women who have a familial history of malignancy.[3] Yet, estrogens,[3] as well as androgens,[4] may be used in the treatment of inoperable breast cancer, and estrogenic materials are effective in the palliation of prostatic carcinoma and its metastases and may also be useful against lung and skin metastases.[3] Such facts have led us to propose that the aza analogs of the steroids might be of considerable interest as possible carcinolytic agents.[5] Perhaps an azasteroid would fit the enzyme site of the parent hormone in such a manner that only a carcinolytic effect would result.

The favorable effect of estrogens upon the blood levels of cholesterol and presumably upon the course of atherosclerosis[6] raises the question of whether or not an azaestrogen would retain the antiatherogenic effect of the parent hormone without exhibiting the undesirable estrogenic effect. It is possible that a nonestrogenic azasteroid would

(1) Abstracted from a portion of the Ph.D. thesis of John A. Durden, Jr., University of Kansas, 1957.

(2) This investigation was supported in part by Grant CY-3573, from the National Cancer Institute, U. S. Public Health Service.

(3) *New and Nonofficial Drugs*, J. P. Lippincott Co., Philadelphia, Pa., 1959, p. 504.

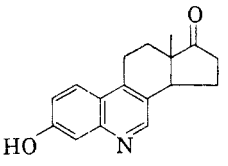
(4) *New and Nonofficial Drugs*, J. P. Lippincott Co., Philadelphia, Pa., 1959, p. 542.

(5) Application for Research Grant to the National Institutes of Health, February 26, 1957.

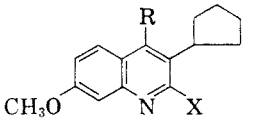
(6) H. W. Eder in *Hormones and Atherosclerosis*, G. Pincus, Ed., Academic Press, Inc., New York, N. Y., 1959, Chapter 24.

fit an enzyme site important to cholesterol synthesis in such a manner that the generation of cholesterol would be inhibited.

These considerations have induced us to undertake various syntheses designed to lead to a number of azasteroids. Recent publications from other laboratories have prompted a preliminary report of incomplete work toward a total synthesis of 6-azaequilenin (I).[7]



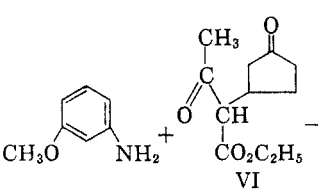
I



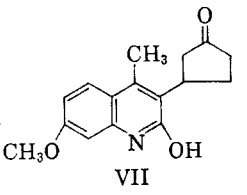
	R	X
II.	CH_2CH_3	OH
III.	CH_3	OH
IV.	CH_3	Cl
V.	CH_3	H

Model compound II was made by means of the Knorr quinoline synthesis[11] which entailed heating a mixture of *m*-anisidine and ethyl α-cyclopentylpropionylacetate[12] to give an anilide which was closed by sulfuric acid to 3-cyclopentyl-7-methoxy-4-ethylcarbostyril (II). The same reactions involving *m*-anisidine and ethyl α-cyclopentylacetoacetate[12a] gave α-cyclopentylacetoaceto-*m*-anisidide. Treatment of the anisidide with sulfuric acid gave 3-cyclopentyl-7-methoxy-4-methylcarbostyril (III). Reaction of III with phosphorus oxychloride gave the gummy 2-chloroquinoline (IV) which, through hydrogenolysis using palladium on charcoal, afforded 3-cyclopentyl-7-methoxylepidine (V) as the hydrochloride.

A closer approach to I was through the synthesis of 3-(3-oxocyclopentyl)-7-methoxy-4-methylcarbostyril (VII). Ethyl α-(3-oxocyclopentyl)-acetoacetate (VI) was synthesized by the Michael condensation using 2-cyclopentenone[13] and aceto-



VI



VII

acetic ester. From *m*-anisidine and VI in the Knorr reaction, the carbostyril (VII) was obtained. VII formed a 2,4-dinitrophenylhydrazone.

Carbostyrils II, III, and VII have very similar infrared spectra, with lactam peaks (1650 cm.$^{-1}$)[14] but only VIII has carbonyl absorption (1740 cm.$^{-1}$) which is due exclusively to the terminal ring ketonic grouping. The lepidine (V) showed no lactam absorption.

Attempts are currently being made to improve the yield of VII; and other studies are in progress toward the synthesis of 6-azaequilenin and other azasteroids.

EXPERIMENTAL

3-Cyclopentyl-7-methoxy-4-ethylcarbostyril (II). A mixture of 14 g. (0.067 mol.) of ethyl α-cyclopentylpropionylacetate[12] and 10 g. (0.067 mol.) of *m*-anisidine was heated at reflux temperature with a Bunsen burner for 5 min. After the mixture had been cooled, 40 ml. of concentrated sulfuric acid was added very slowly with stirring. During the treatment a solid separated, the mixture became very hot and the the solid redissolved while a vigorous ebullition took place. After standing 40 min. at room temperature, the reaction mixture was heated on the steam bath for 20 min. before it was poured with stirring into ice water. A purple solid separated. The suspension was made neutral with sodium hydroxide and a solid was collected on a filter and subsequently recrystallized from alcohol with charcoal treatment to yield 2 g. (11% yield) of a white solid, II, m.p. 200–201°. Further recrystallization from alcohol elevated the melting point to 204–205°.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 75.30; H, 7.70.

α-Cyclopentylacetoaceto-m-anisidide. A mixture of 19.8 g. (0.1 mol.) of ethyl α-acetylcyclopentylacetate[12a] and 12.3 g. (0.1 mol.) of *m*-anisidine[15] was heated at reflux temperature under an air condenser for 4 min. with a Bunsen burner. During this period, fumes came from the condenser. The contents of the flask were poured into a beaker, and cooling in an ice bath gave a solid which was collected on a filter. The product was triturated with Skelly B to yield 14 g. (51%) of white anisidide, m.p. 130–133°. Recrystallization from benzene-Skelly B elevated the melting point to 133–134.5°. $\lambda_{max}^{CHCl_3}$ 1680 cm.$^{-1}$ (C=O sec. amide I); 1600 cm.$^{-1}$ (sec. amide II); 1530 cm.$^{-1}$ (sec. amide II); 1280 cm.$^{-1}$ (sec. amide III).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.63; H, 7.69. Found: C, 69.53; H, 7.68.

3-Cyclopentyl-7-methoxy-4-methylcarbostyril (III). A mixture of 14.7 g. (0.07 mol.) of ethyl α-cyclopentylaceto[12a] and 9.1 g. (0.07 mol.) of *m*-anisidine[15] was heated at reflux under an air condenser with an open flame for 3 min. and was then

(7) Several steroid analogs with a five-membered heterocyclic B ring have been synthesized.[8] A 3-aza-A-homocholestanone has been prepared through partial synthesis from cholestanone,[9] and a synthetic approach has been made toward a 14-aza-D-homosteroid.[10]

(8) G. V. Bhide, M. R. Pai, N. L. Tikotkar, and B. D. Tilak, *Tetrahedron*, **4**, 420 (1958); G. V. Bhide, N. L. Tikotkar, and B. D. Tilak, *Chemistry and Industry*, 1319 (1957); R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Research (India)*, **15B**, 497, 573 (1956) [*Chem. Abstr.*, **51**, 5784, 8719 (1957)]; R. J. Collins and E. V. Brown, *J. Am. Chem. Soc.*, **79**, 1103 (1957).

(9) C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.*, 3458 (1958).

(10) N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(11) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1952, Vol. 4, p. 30.

(12) Prepared by the methods of (a) H. Rydon, *J. Chem. Soc.*, 1544 (1939), and (b) F. Challenger and B. Fishwick, *J. Inst. Petrol.*, **39**, 220 (1953) [*Chem. Abstr.*, **48**, 9355 (1954)].

(13) M. Rosenblum, *J. Am. Chem. Soc.*, **79**, 3179 (1957), and K. Alder and R. Flock, *Chem. Ber.*, **89**, 1735 (1956).

(14) *Cf.* J. A. Gibson, W. Kynaston, and A. S. Lindsay, *J. Chem. Soc.*, 4340 (1955), who have shown that carbostyrils exist as 2-quinolones whose spectra confirm the amido form in neutral or acidic media. Also, G. W. Ewing and E. A. Steck, *J. Am. Chem. Soc.*, **68**, 2181 (1946), have used ultraviolet spectra to demonstrate the amido structure.

(15) F. Reverdin and A. de Luc, *Ber.*, **47**, 1537 (1914).

allowed to cool at room temperature. The mixture was then added slowly to 15 ml. of sulfuric acid preheated to 60°, at such a rate that the temperature did not rise above 90°. When addition was complete the temperature of the reaction mixture was held at 90° for 20 min. and then allowed to fall to 60° when the mixture was poured with vigorous stirring over ice. The solid which separated was collected on a filter and then recrystallized from 500 ml. of alcohol with charcoal treatment to give 5.4 g. (30% yield) of a white solid (III), m.p. 216–218°. After further recrystallization it melted at 218–219°.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.79; H, 7.44. Found: C, 74.83; H, 7.25.

α-Cyclopentylacetoaceto-*m*-anisidide which had been isolated was also converted in about 50% yield by treatment with sulfuric acid to III.

3-Cyclopentyl-7-methoxylepidine hydrochloride monohydrate (V). A mixture of 5.43 g. (0.021 mol.) of III and 5 ml. of phosphorus oxychloride was heated on a steam bath for about 30 min. until complete solution had almost taken place. The reaction mixture was heated at gentle reflux for 15 min. with a Bunsen burner and then it was poured into water with stirring. A solid separated which was collected on a filter and subsequently dissolved in chloroform. The solution was washed with water, and then dried over a sodium sulfate–sodium carbonate mixture. The drying agent was removed by filtration and the chloroform was removed *in vacuo* to leave a residual gum. The residue was dissolved in 40 ml. of glacial acetic acid. After the addition of 2 g. of anhydrous sodium acetate and 1 g. of 5% palladium on charcoal, hydrogenation was carried out at 35 lb. pressure with heat supplied to the flask by an infrared lamp. When the theoretical amount of hydrogen had been absorbed, the catalyst was removed and the volume of the filtrate was reduced. The residue was made basic with alkali. Extraction with ether and drying over a sodium hydroxide–sodium sulfate mixture gave an ether solution which was treated with hydrogen chloride gas to produce a solid. Recrystallization from alcohol gave 4 g. (70% yield) of off-white crystalline V, m.p. 210–211°.

Anal. Calcd. for $C_{16}H_{19}NO{\cdot}HCl{\cdot}H_2O$: C, 64.96; H, 7.50. Found: C, 65.05; H, 7.50.

Ethyl α-(3-oxocyclopentyl)acetoacetate (VI). A solution of 1.15 g. (0.05 atom) of sodium metal in 100 ml. of absolute alcohol was reduced in volume to dryness and the residue taken up in 4 ml. of absolute alcohol. Then a mixture of 22 g. (0.27 mol.) of 2-cyclopentenone[13] and 59.5 g. (0.46 mol.) of ethyl acetoacetate was added to the alcoholic solution with shaking. An exothermic reaction occurred. After 30 min. at room temperature, the reaction mixture was warmed at 45° for 2 hr. and then left at room temperature overnight. The reaction mixture was made neutral with 3.5 ml. of glacial acetic acid, diluted with 200 ml. of ether, and extracted twice with water. The ether extract was dried over sodium sulfate. Removal of the drying agent and distillation gave 38 g. (67% yield) of clear liquid (VI), b.p. 135° (1.5 mm.); n_D^{23} 1.4650. $\lambda_{max}^{CHCl_3}$ 1718 cm.$^{-1}$ (C=O); 1740 cm.$^{-1}$ (5-membered ring C=O); 1742 cm.$^{-1}$ (ester C=O); 1625 cm.$^{-1}$ (ester C=O chelated to enolic OH?).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.32; H, 7.79.

3-(3-Oxocyclopentyl)-7-methoxy-4-methylcarbostyril (VII). A mixture of 5 g. (0.023 mol.) of ester VI and 2.9 g. (0.024 mol.) of *m*-anisidine was heated at reflux temperature over an open flame for 2.75 min. The thick red oil was poured into a beaker and allowed to cool. The oil was then chilled in ice and treated slowly with 23 ml. of concentrated sulfuric acid with stirring. The acid solution was left in ice for about 30 min., warmed on the steam bath for 10 to 15 min. and then poured with vigorous stirring over ice whereupon a gum separated. The suspension was made basic with sodium hydroxide solution so that the mixture became warm and the gum turned slightly crystalline. The mixture was neutralized with 10% hydrochloric acid and chilled in the ice bath for 3 hr. The solid was collected on a filter. Recrystallization from a 20:1 ethyl acetate–alcohol mixture gave a white solid (VII), m.p. 177–178°, 1 g. (15% yield).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.56; H, 6.32.

The *2,4-dinitrophenylhydrazone* of VII was prepared and recrystallized from acetic acid,[16] m.p. 275–277° (dec.).

Anal. Calcd. for $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69. Found: C, 58.13; H, 4.66.

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(16) By Mr. D. G. Mikolasek.

The Color of 8-Mercaptoquinoline

J. E. BANFIELD

September 22, 1959

The absorption spectrum of 8-mercaptoquinoline in ethanol and in 50% ethanol has been reported by Badger and Buttery[1] and observations concerning its thermochromic solution in chloroform containing a little ethanol were made. These workers considered that the C=C—C=S chromophore was not involved.

Very recently the absorption spectrum of 8-hydroxy-1-methylquinolinium anhydro salt (and of related compounds) in a number of solvents has been reported[2] together with some observations of the colors. Thus the hydrated 8-hydroxy-1-methylquinolinium hydroxide was orange, and this on dehydration changed to violet-red. The solution of the anhydro salt in water was red, in nonpolar solvents was violet, and the addition of hydroxylic solvents to the chloroform solution resulted in a progressive hypsochromic shift. End absorption in the visible was recorded for the acidic solution. A lucid explanation of these facts in terms of the resonance contributors (Ia), (Ib), *etc.*, the modification of these by hydrogen bonding at the oxygen atom, and of protonation of the oxygen atom has been presented.[2]

The generally similar shape of the spectra and the relative positions of the long wave length maxima of the 8-hydroxy-1-methylquinolinium anhydro salt (484 mμ)[2] and of the 8-mercaptoquinoline (500 mμ)[1] in ethanol together with some findings made during another investigation prompt us to record these observations in support of a parallel explanation of the properties of 8-mercaptoquinoline in terms of the resonance contributors (IIa), (IIb), *etc.* Thus the concentrated solution of 8-mercaptoquinoline in pyridine was an intense blue-violet which was changed by the addi-

(1) G. M. Badger and R. G. Buttery, *J. Chem. Soc.*, 3236 (1956).

(2) J. P. Saxena, W. H. Stafford, and Winifred L. Stafford, *J. Chem. Soc.*, 1579 (1959).