solid (1.4 g.). This was recrystallized from propionic acids as rods of m.p. 274–275°.

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.0; H, 6.1; N, 13.1. Found: C, 70.4; H, 5.9; N, 13.4.

Oxidation of IIa.—To a suspension of 2-amino-4-benzoyl-5-phenylimidazoline-2 (5.0 g.) in 10% sodium carbonate solution (120 cc.) was added potassium permanganate (2.2 g.) and the mixture heated under reflux for 30 min. The mixture was steam distilled to give a few drops of a heavy oil smelling strongly of bitter almonds. Treatment of the oil with 2,4-dinitrophenylhydrazine reagent gave an orange 2,4-dinitrophenylhydrazone of m.p. 236–237°, undepressed on admixture with an authentic sample of benzaldehyde 2,4-dinitrophenylhydrazone.

2-Dimethylamino-4-benzoyl-5-phenylimidazoline-2. (IIb) was prepared by the same general method as IIa from 1-benzoyl-2-phenylethylene oxide (10 g.) and N,N-dimethylguanidine (4.5 g.) in ethanol (120 cc.). The solid (10.5 g. 81%) was recrystallized from ethanol as colorless needles of m.p. 284–285°. The analytical sample was purified by sublimation.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.7; H, 6.5; N, 14.3. Found: C, 73.9; H, 6.5; N, 14.4. Infrared Spectrum for II (b): 3180, 2887, 1670, 1636, 1502, 1461, 1412, 1328, 1303, 1232, 1198, 1088, 1056.

Treatment of II (b) with picric acid gave the picrate as yellow needles of m.p. 207–209°, purified by recrystallization from ethanol.

Anal. Calcd. for $C_{24}H_{22}N_6O_8$: C, 55.2; H, 4.2; N, 16.1. Found: C, 55.4; H, 4.3; N, 16.2.

2-Cyclohexylamino-4-benzoyl-5-phenylimidazoline-2 IIc was prepared as for IIa using 1-benzoyl-2-phenylethylene oxide (5 g.) and a solution of cyclohexylguanidine (3 g.) in ethanol (60 cc.). The solid (6.7 g., 82%) was purified by recrystallization from aqueous acetic acid to give colorless needles of m.p. 291–292°.

Anal. Calcd. for $C_{22}H_{25}N_3O$: C, 76.0; N, 7.2; N, 12.1. Found: C, 75.5; H, 7.2; N, 12.3.

Treatment with picric acid yielded the picrate as yellow needles of m.p. 214–216°, purified for analysis by recrystallization from ethanol.

Anal. Calcd. for $C_{28}H_{28}N_6O_8$: C, 58.3; H, 4.9; N, 14.6. Found: C, 58.1; H, 4.9; N, 14.5.

2-N-Piperidino-4-benzoyl-5-phenylimidazoline-2 IId was prepared from 1-amidinopiperidine (3 g.) in ethanol (30 cc.) and 1-benzoyl-2-phenylethylene oxide (7 g.) by the usual method. The solid (8.7 g., 95%) was recrystallized from aqueous acetic acid as colorless plates of m.p. > 300°.

Anal. Calcd. for $C_{21}H_{23}N_3O$: C, 73.7; H, 7.0; N, 12.3. Found: C, 73.9; H, 6.9; N, 12.4. Infrared spectrum: 3320, 3140, 3080, 1668, 1595, 1502, 1461, 1435, 1356, 1340, 1325, 1300, 1215, 1204, 1165.

Oxidation of IId.—A suspension of IId (6.5 g.) in 10% sodium carbonate solution (100 cc.) was refluxed with potassium permanganate (2 g.) for 30 min. then steam distilled to give a few drops of benzaldehyde, identified by its odor and the formation of a 2,4-dinitrophenylhydrazone of m.p. 235–237°, which gave no depression on admixture with an authentic sample.

Attempted Acylation of IIb, c, and d.—One gram of each of IIb, c, and d was refluxed individually for 6 hr. with a 1:1 ratio by volume of acetic acid–acetic anhydride (10 cc.), cooled, and poured into ice–water. In all cases only starting material was recovered, identified by m.p. and mixed m.p.

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Cleavage of Steroidal Digitonides in Dimethyl Sulfoxide

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In connection with another problem under investigation in this laboratory, it became desirable to develop a procedure for cleavage of steroidal digitonides and recovery of the sterol directly by extraction. We now wish to report the following rapid and convenient method.

Dimethyl sulfoxide, in which cholesterol and cholestanol are sparingly soluble, exhibits remarkable solvent power for digitonin and brings about complete dissociation of digitonides at steam-bath temperature. When the solution is allowed to come to room temperature, the sterol precipitates and is extracted with hexane. Recovery of the sterol is nearly quantitative, and the saponin, which remains in the dimethyl sulfoxide layer, may be obtained in good yield by evaporation of the solution to dryness.

Heretofore, pyridine has been the preferred solvent for cleavage of digitonides according to the method originally introduced by Schoenheimer and Dam,[1] and later modified by Bergmann.[2] This method has proved to be reliable, but is often tedious and time consuming.

The use of dimethyl sulfoxide has the distinct advantage of convenience and speed in the isolation of digitonin precipitable sterols. The method also gives excellent results in the decomposition of cholesterol complexes with tomatine and holothurin.[3]

Experimental[4]

Cleavage of Digitonides.—The general procedure is illustrated by the following example. A mixture of dimethyl sulfoxide[5] (20 ml.) and cholesteryl digitonide (1.006 g.) was heated on the steam bath for 15 min.[6] and the resulting solution allowed to come to room temperature, whereupon cholesterol precipitated. The mixture was transferred to a separatory funnel and extracted with 70 ml. of *n*-hexane. The dimethyl sulfoxide layer was extracted further with four 30-ml. portions of *n*-hexane and the combined hydrocarbon layers were allowed to stand for 20 min. over sodium sulfate (15 g.), filtered, and evaporated to dryness. The residue was dried to constant weight (100°/1 mm.) giving cholesterol (0.227 g., 94% recovery) melting at 147–148.5° (m.m.p., infrared spectrum). Evaporation of the dimethyl

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(3) J. D. Chanley, R. Ledeen, J. Wax, R. F. Nigrelli, and H. Sobotka, *J. Am. Chem. Soc.*, **81**, 5180 (1959).

(4) The skillful technical assistance of Mr. Steven Frank is gratefully acknowledged.

(5) Supplier: Crown Zellerbach, Chemical Products Div., Camas, Wash.

(6) In more recent experiments the heating period has been reduced to five minutes with equally good results.

sulfoxide layer to dryness (100°/1 mm.) followed by trituration of the residue with dry ether gave 0.62–0.70 g. of digitonin.

The same procedure applied to cholestanyl digitonide (1.035 g.) gave cholestanol (0.240 g., 97% recovery) melting at 140–142° (m.m.p., infrared spectrum).

Cleavage of Cholesteryl Tomatide.—Treatment of the cholesterol–tomatine complex (1.000 g.) by the procedure described above gave 0.253 g. cholesterol (93% recovery).

Determination of the Molecular Ratio in Cholesterol Holothuride.—Treatment of cholesteryl holothuride[3] (1.000 g.) with dimethyl sulfoxide gave cholesterol (0.389 g.). These data give a value of 2:1 for the molar ratio of cholesterol: holothurin[7] in the complex.

(7) The calculations have been based on a molecular weight of 1190 for holothurin. See ref. 3.

The Synthesis of 3,19-Dioxo-4-androsten-17β-ol[1]

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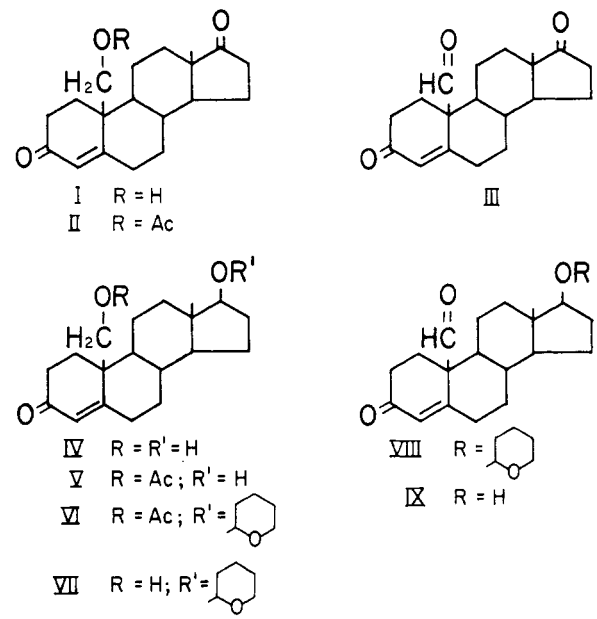
Earlier investigations have shown that incubation of C^{14}-labeled testosterone with normal human ovarian tissue converted it into C^{14}-labeled estradiol-17β.[2,3] In the biosynthetic transformation of androgens to estrogens the following sequence has been established: androgens → 19-hydroxy compounds → 19-aldo compounds → estrogens. However, when testosterone 4-C^{14} was incubated with certain human polycystic ovarian tissues, primarily 19 - hydroxy - 4 - androstene - 3,17 - dione (I), 19-hydroxytestosterone (IV), and 3,17,19-trioxo-4-androstene (III) were obtained and no estrogens were discernable.[3] Furthermore, radioactive metabolites isolated from these studies presented strong presumptive evidence for the presence of 3,19-dioxo-4-androsten-17β-ol (IX). A search of the literature revealed that this compound has not been synthesized and in view of its potential role in the steroid metabolism we wish to report its synthesis.

In the first instance we decided to study the reduction of 3,17,19-trioxo-4-androstene (III), with one equivalent of sodium borohydride under the conditions described by Norymberski[4] to achieve the specific reduction of the 17-keto group. In view



of the steric considerations and the tertiary nature of the C-19 aldehyde function, we anticipated that preferential reduction of the 17-ketone would occur without effecting the aldehyde group.

Oxidation of 19-hydroxy-4-androstene-3,17-dione (I) with 8 *N* chromic acid,[5] instead of chromium trioxide in acetic acid,[6] gave a much superior yield (90%) of 3,17,19-trioxo-4-androstene (III). Reduction of III with one equivalent of sodium borohydride in methanol,[4,7] contrary to our expectations (*supra*), gave a mixture of 19-hydroxytestosterone (IV) and 19-hydroxy-4-androstene-3,17-dione (I). Apparently, the primary attack of borohydride appears to be on the C-19 aldehyde function rather than on the C-17 ketone.

Another approach to the synthesis of IX was then investigated which resulted in its successful synthesis. 19 - Acetoxy - 4 - androstene-3,17 - dione (II),[8] was treated with one equivalent of sodium borohydride in methanol at 0° to give 17β-hydroxy-19-acetoxy-4-androsten-3-one (V, 19-acetoxytestosterone). The 17-hydroxyl function in V was then protected as the tetrahydropyranyl ether which is stable to alkali but can easily be hydrolyzed with acid. Compound V was stirred at room temperature with dihydropyran[9] in the presence of a cationic resin (Amberlite IR-120) to give 19-acetoxy-4-androsten - 3 - one - 17β - (2′ - tetrahydropyranyl) ether (VI). The 19-acetoxy group in VI was then

(1) This investigation was supported by a Grant A-3270 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

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