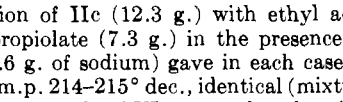
acetal, (8) glyoxal, (9) dimethylacetylene dicarboxylate and sodium alkoxide, (10) acetic anhydride, (11) oxalyl chloride with boron trifluoride or phosphorus oxychloride, and (12) chloroform and sodium alkoxide.

Attempted reaction of IIc (12.3 g.) with ethyl acetoacetate (8.2 g.) or ethyl propiolate (7.3 g.) in the presence of sodium methoxide (from 4.6 g. of sodium) gave in each case only compound VI (1–2 g.), m.p. 214–215° dec., identical (mixture melting point, spectra) with a sample of VI prepared as described above, in addition to much red-brown, intractable gum.

The reaction of IIc (5.4 g.) with acetic anhydride (7.5 g.) and boron trifluoride etherate (23 ml.) did not lead to VIIc, but rather there was isolated, after hydrolysis with sodium acetate solution, extraction, trituration with ether–ethyl acetate, and recrystallization from methanol, a pale yellow, crystalline compound: m.p. 179–181° dec.; λ_{max}^{Nujol} 6.11 and 6.40–6.51 μ; λ_{max}^{EtOH} 255 and 352 mμ (ε 13,810 and 11,710, respectively) with an inflection *ca.* 300 mμ (ε 5060).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.91; H, 4.88; N, 4.96.

The formula and spectra of this substance lead to a first (tentative) assignment of its structure as either **1-methyl-2-nitro-3-acetonyl-5,6-methylenedioxyindene** or **1-methyl-2-acetyl-3-nitromethyl-5,6-methylenedioxyindene**, in either of which the



group relationship might be responsible for the abnormally long wave length of carbonyl infrared absorption.

Acknowledgment.—The laboratory work was done with the technical assistance of Mrs. Ruth Ann MacAllister. We also thank Mr. Louis F. Dorfman, Mr. George Robertson, Mr. Rudolf Oeckinghaus, Miss Natalie Cahoon, Miss Jan Siragusa, and other members of the Technical Services Laboratories for microanalytical and spectral data, and Mrs. Angelina Aretakis for aid in checking the literature.

A Convenient Synthesis of 3β-Hydroxyandrost-4-en-17-one[1a]

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3β-Hydroxyandrost-4-en-17-one (**1**) was synthesized by reduction of 17-hydroxypregn-4-ene-3,20-dione (**2**) with lithium tri-*t*-butoxyaluminohydride, followed by side-chain cleavage with lead tetraacetate. This method yields almost exclusively the 3β-hydroxy epimer (**1**) uncontaminated with saturated 3-hydroxy-5α-androstan-17-one.

3β-Hydroxyandrost-4-en-17-one (**1**), although it is known, is not readily obtained in pure form. Because of its formation from androst-4-ene-3,17-dione in the presence of reduced diphosphopyridine nucleotide and an acetone powder of sheep adrenal microsomes,[2a] it became necessary to prepare a pure sample for comparison and for further biochemical studies. The allylic alcohol **1** and similar compounds have recently become prominent in the consideration of metabolic pathways and the mechanism of enzymic reduction of Δ^4-3-keto steroids.[2b]

The method of Ruzicka, *et al.*,[3] involving addition of hydrogen chloride to 3β-hydroxyandrost-5-en-17-one followed by dehydrochlorination, appeared to be inconvenient and might be expected to yield a mixture of Δ^4 and Δ^5 isomers.

Reduction of androst-4-ene-3,17-dione with sodium borohydride in 2-propanol, under the conditions described by Kupfer[4] as suitable for the conversion of pregn-4-ene-3,20-dione to 3β-hydroxypregn-4-en-20-one, apparently caused reduction of the 17-ketone at approximately the same rate as the 3-ketone, as evidenced by the parallel diminution of the infrared absorption intensities at 1740 and 1675 cm.$^{-1}$. A more indirect but successful route (Scheme I) involved reduction with lithium tri-*t*-butoxyaluminohydride[5,6] of 17-hydroxypregn-4-ene-3,20-dione (**2**) to a mixture of pregn-4-ene-3β,17,20-triols (**3**) epimeric at C-20. The 17,20-glycol was cleaved by lead tetraacetate in glacial acetic acid to yield the 17-ketone.[7] The product **1** was converted to 3β-benzoyloxyandrost-4-en-17-one (**4**), which crystallized readily from methanol or acetone. Hydrolysis then yielded the free 3β-hydroxyandrost-4-en-17-one (**1**) which, after several crystallizations from hexane, melted at 133.5–134°.

During the course of this work, Thomas and Dorfman[8] described a similar synthesis of 3β-hydroxyandrost-4-en-17-one (**1**) using sodium borohydride in methanol for the reduction. They obtained a product of somewhat lower melting point (124°). In our experience, borohydride reduction of 17-hydroxypregn-4-ene-3,20-dione (**2**) in 95% ethanol or 2-propanol, followed by lead tetraacetate cleavage, gives a mixture of 3β-hydroxyandrost-4-en-17-one (**1**, 70%) and the saturated 3β-hydroxy-5α-androstan-17-one (20%) together with minor quantities of other products. 3β-Hydroxy-5α-androstan-17-one has a mobility very close to that of the allylic alcohol **1** in several thin layer chromatographic systems; its presence is readily detected by gas–liquid chromatography. Sondheimer,

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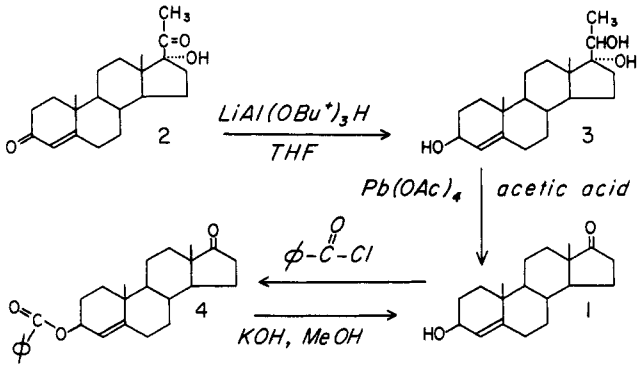
SCHEME I

PARTIAL SYNTHESIS OF 3β-HYDROXYANDROST-4-EN-17-ONE



et al.,[9,10] have reported that treatment of androst-4-ene-3,17-dione and progesterone 20-cycloethylene ketal with sodium borohydride in aqueous alcohols leads to partial reduction of the double bond.

The use of lithium tri-*t*-butoxyaluminohydride not only avoided reduction of the double bond,[6,11] but also gave greater stereospecificity of α-attack on the ketone. Wheeler and Mateos[5] found that the butoxyhydride reagent reduced cholestenone to give 99% of cholest-4-en-3β-ol, while lithium aluminum hydride in ether[12] gave only 74% of the 3β-allylic alcohol. In our case, reduction of 17-hydroxypregn-4-ene-3,20-dione (**2**) with lithium tri-*t*-butoxyaluminohydride gave only a trace (<1%) of contaminant that may be the 3α-allylic alcohol; on reduction with $LiAlH_4$ in ether or diglyme at room temperature the corresponding contaminant constituted 30% of the product.

That the product **1** was in fact a 3-hydroxyandrost-4-en-17-one was established by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone[13] to androst-4-ene-3,17-dione. The crude product, after one crystallization from acetone, had λ_{max} 240 mμ (ε 17,300), compared to the published[14] value of λ_{max} 240 mμ (ε 17,170) for pure androst-4-ene-3,17-dione. This indicates little contamination with saturated 3-hydroxyandrostan-17-one, which would not have been oxidized to a conjugated enone under these conditions.

Acid-catalyzed dehydration of the allylic alcohol **1** afforded androsta-3,5-dien-17-one[15]; under the same conditions, 3β-hydroxyandrost-5-en-17-one was not appreciably dehydrated.[16]

The β-orientation of the 3-hydroxyl group of **1** was established by its precipitation with digitonin and by the molecular rotation change (−182°) in passing from androst-4-ene-3,17-dione to 3-hydroxyandrost-4-en-17-one. This corresponds closely to the change observed in the cholest-4-en-3-one → cholest-4-en-3β-ol (−167°) and 17β-hydroxyandrost-4-en-3-one → androst-4-ene-3β,17β-diol (−177°) series, and is in marked contrast to the known changes in molecular rotation in passing from the enones to the corresponding 3α-allylic alcohols in those series. Confirmation of the β-orientation of the 3-hydroxyl group in **1** was obtained by examination of the n.m.r. absorption of the compound. The peak at δ = 5.32 p.p.m. can be assigned to the vinyl 4-hydrogen; it appears as a doublet of $J < 2$ c.p.s.[17]

Experimental

Melting points were measured on a Kofler apparatus. Optical rotations were determined in chloroform solution, ultraviolet spectra in 95% ethanol, infrared spectra in carbon disulfide, and n.m.r. spectra in deuteriochloroform with tetramethylsilane as internal reference. Thin layer chromatograms were run on silica gel G (Brinkmann Instruments), and steroids were detected by spraying with a 1:1 solution of concentrated sulfuric acid–ethanol followed by heating for 10 min. at 110°. A single column of 2% SE30 on Anakrom ABS (80–90 mesh) at 230° and 100 ml./min. gas flow was used for gas chromatography.

3β-Benzoyloxyandrost-4-en-17-one (4).—17-Hydroxypregn-4-ene-3,20-dione (**2**, 5 g.) was dried by dissolving in benzene and evaporating the solvent. Tetrahydrofuran (250 ml., freshly distilled from sodium) was added, and the mixture was stirred to dissolve the steroid. The flask was sealed with a mercury trap, lithium tri-*t*-butoxyaluminohydride (25 g.) was added, and the mixture was stirred at 0° overnight.[18,19] A sample of the solution then showed virtually no absorption at 240 mμ. The mixture was partitioned between ethyl acetate and water, and the ethyl acetate phase was washed several times with sodium bicarbonate solution and with water. The ethyl acetate extract yielded needle-like crystals on standing overnight at room temperature. They were collected, washed with ethyl acetate, and dried (yield 2.76 g.). A second crop (0.8 g.) was also collected (total yield 71%). Infrared analysis showed that a slight amount of Δ^4-3-ketone, but no 20-ketone, remained. The product, a mixture of pregn-4-ene-3β,17,20-triols (**3**), was not purified further.

Part of the combined first and second crops of the triols (**3**, 3 g.) was dissolved in glacial acetic acid, and lead tetraacetate (9 g.) was added. After stirring for 45 min., ethylene glycol (15 ml.) was added to remove excess lead tetraacetate, and the mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate phase was washed twice with sodium bicarbonate solution and three times with water. It was then dried with sodium sulfate and the solvent was evaporated under reduced pressure. A sample of the remaining oil was examined by thin layer chromatography in the solvent system ether–benzene, 2:1. The major product was the desired 3β-hydroxyandrost-4-en-17-one (**1**), with slight contamination by starting material **3**, by androsta-3,5-dien-17-one, and by an unidentified compound traveling slightly behind **1** (probably 3α-hydroxyandrost-4-en-17-one).[20] Gas chromatography revealed that no 3β-hydroxy-5α-androstan-17-one was present in the mixture.

The oil was dissolved in pyridine (6 ml.) and redistilled benzoyl chloride (5 ml.) was added. The flask was stoppered and left overnight. Water was then added and the mixture was extracted with ethyl acetate. The extract was washed with sodium bicarbonate and water, dried with sodium sulfate, and evaporated under reduced pressure. The residual oil was dissolved in methanol and the solvent was again evaporated to eliminate any remaining pyridine. Thin layer chromatography (cyclohexane–ethyl acetate, 3:1) showed that no free allylic alcohol **1** remained. The benzoate **4** contained traces of androsta-3,5-dien-17-one and androst-4-ene-3,17-dione. The product **4** was crystallized from methanol, acetone, and then methanol to yield pure 3β-benzoyloxyandrost-4-en-17-one (**4**): m.p. 190–191°; 1.46 g., 41.5% yield based on the pregn-4-en-3β,17,20-triols; $[\alpha]_D$ +46°; λ_{max} 282 mμ (ε 700), 273 (890), and 229 (13,600); ν_{max} 1743 (17-ketone), 1720 (3-benzoate), 1270, and 1250 cm.$^{-1}$ (also 3-benzoate), no free hydroxyl band.

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(16) See, however, M. S. Patel and W. J. Peal, *Tetrahedron*, **20**, 2499 (1964).

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(20) See ref. 2b.

Anal. Calcd. for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.64; H, 8.07.

3β-Hydroxyandrost-4-en-17-one (1).—The benzoate **4** (725 mg.) was hydrolyzed overnight with 5% potassium hydroxide in aqueous methanol under a nitrogen atmosphere. The solution was diluted with water and the product was extracted into ethyl acetate, washed with sodium bicarbonate solution and with water, dried over sodium sulfate, and evaporated to an oil. Repeated crystallizations from hexane gave the analytical sample of 3β-hydroxyandrost-4-en-17-one (**1**, 198 mg., 37% yield based on 3β-benzoyloxyandrost-4-en-17-one) m.p. 133.5–134° undepressed on admixture with an authentic sample[21] (lit.[3] m.p. 128.5–130°); $[\alpha]_D$ +134°; λ_{max} no selective absorption; ν_{max} 3450 (hydroxyl), 1744 (17-ketone), and 854 cm.$^{-1}$ (C=C—H); n.m.r. δ = 0.88 (singlet), 1.08 (singlet), 1.55 (singlet), 4.1 (probably quintet), and 5.32 (doublet, 1H) p.p.m.

Anal. Calcd. for $C_{19}H_{28}O_2$; C, 79.12; H, 9.79. Found: C, 78.98, 78.54; H, 7.92, 9.53.

The pure allylic alcohol in ethanol solution slowly underwent oxidation to androst-4-ene-3,17-dione. However, it was stable in the crystalline state. Exposure to acid or passage through a gas–liquid chromatograph or alumina column partially dehydrated the compound to form a substance corresponding in mobility to androsta-3,5-dien-17-one.

3β-Hydroxyandrost-4-en-17-one (1) was precipitated by digitonin.[22]

(21) We thank Dr. Joseph S. Mihina of G. D. Searle and Co. for the sample of 3β-hydroxyandrost-4-en-17-one.

Androst-4-ene-3,17-dione.—The allylic alcohol **1** (47 mg.) was dissolved in dioxane (twice distilled from sodium), and 2,3-dichloro-5,6-dicyanobenzoquinone (55 mg.) was added. After standing overnight the mixture was diluted with methylene chloride and applied to a column of activity III alumina (3 g.), and the steroids were eluted with methylene chloride (150 ml.). The product was shown by thin layer chromatography (cyclohexane–ethyl acetate, 3:1) to contain at least 95% androst-4-ene-3,17-dione, with only traces of a more mobile and of a less mobile compound. A single crystallization from acetone yielded androst-4-ene-3,17-dione: m.p. 170–172°, undepressed on admixture with an authentic sample of m.p. 169–172°; λ_{max} 240 mμ (ε 17,300); the infrared spectrum was identical with that of authentic material.

Androsta-3,5-dien-17-one.—The allylic alcohol **1** (96 mg.), was refluxed under nitrogen with 5 *N* sulfuric acid (7 ml.) and 95% ethanol (20 ml.) for 45 min. Water was added and the reaction mixture was extracted with ethyl acetate, washed with water, and dried with sodium sulfate. The solvent was evaporated and the residue was shown to be homogeneous by gas chromatography and thin layer chromatography (ether–benzene, 2:1). Crystallization from methanol gave androsta-3,5-dien-17-one: m.p. 85–89° (lit.[23] m.p. 88–89°); λ_{max} 243 mμ (ε 10,700), 235 (15,800), and 228 (14,000); ν_{max} 1743 cm.$^{-1}$ (17-ketone), no free hydroxyl band.

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Conformational Analysis. XXXIX. The Conformations of Ring A in Bromo Derivatives of Cholestan-3-one and Related Compounds[1,2]

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The preferred conformations of ring A for a variety of 2- and 4-methylated and brominated steroids have been predicted by *a priori* calculations. In a number of cases the predictions have been checked by experimental measurements, mainly dipole moments and optical rotatory dispersion. The 5-halocholestan-3-ones were also studied.

The previous paper in this series discussed the various possible conformations of cyclohexanone rings and developed methods for the *a priori* calculation of such conformations as they occur in more complicated systems, including in particular methylated derivatives of cholestanone.[1] There are a number of cholestanone derivatives known with bromine at C-2 or C-4, or halogen at C-5, and the conformations of these compounds form the subject of the present paper. Because of the presence of two dipoles, the halo ketones present some complicating features not found in the methyl derivatives studied earlier, but they are experimentally more amenable to study by various physical methods. Most of the necessary numerical data required are available or deducible from earlier studies on cholestanones and/or α-halo ketones. The β-halo ketones require, in addition, the evaluation of the electrostatic interactions between dipoles. The present objectives are to illustrate how the *a priori* calculations for these systems can be carried out, and to make predictions for a variety of systems. In a number of cases these predictions have then been tested experimentally.

(1) Paper XXXVIII: N. L. Allinger, J. Allinger, and M. A. DaRooge, *J. Am. Chem. Soc.*, **86**, 4061 (1964).

(2) This investigation was supported by Public Health Service Research Grant A-5836 from the National Institute of Arthritis and Metabolic Diseases.

The starting point for the calculations was the parent molecule, cholestan-3-one. The conformational energy of the chair form, relative to an arbitrary zero based on cyclohexanone, can be taken as 1.8 kcal./mole, the energy of the C-19 methyl axial to ring A. The second conformation to be considered for cholestanone is the flat chair, in which C-3 has moved upward approximately into the plane of C-1, C-2, and C-4. The energy of this form was calculated to be 3.0 kcal./mole using the methods and numbers developed earlier (the interactions and their corresponding energies are given in Table I). This value is sufficiently close to that of the undeformed chair that it may be expected that the conformation of minimum energy will be between those of the chair and the flat chair, but much nearer the former, and the ordinary chair will therefore be used herein as the best approximation to the real chair.

Lastly, the flexible form of ring A must be considered. Following earlier methods,[1] the various interaction energies as functions of θ were calculated (Table I). The sum of these energies yields a conformation of minimum energy of 4.4 kcal./mole for the flexible form at about θ = 35°, which will again show a wide and unsymmetrical pseudo-rotation, leaning somewhat toward higher values of θ. The flexible form will have a greater entropy than the rigid forms, and this will