Steroids and Related Natural Products. 63. 17β-Acetoxy-4-oxa-2-androstene[1]

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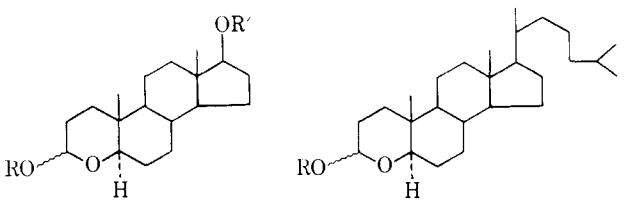
Received March 30, 1970

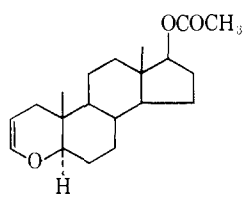
In a prior report we described synthesis of hemiacetal Ia[2a,b] from testosterone. The present extension of this study was undertaken to further evaluate the endocrinological properties of such 4-oxaandrostanes and to explore a series of lactol and lactolide model experiments required during a program concerned with synthesis of bufadienolides.[1] For both purposes A-ring hemiacetal Ia served well.

Allowing hemiacetal Ia to remain in MeOH containing a trace of 48% HBr for 1 hr gave acetal Ib. Methanesulfonate Ic was prepared in pyridine solution using $MeSO_2Cl$ without noticeably affecting the acetal-containing A ring. Acetylating (Ac_2O–pyridine) hemiacetal Ia and recrystallizing the product from MeOH–H_2O yielded methyl acetal Id. That the 3-acetoxy group was so easily displaced by MeOH was readily shown by repeating the acetylation reaction and recrystallizing the product from Me_2CO–pentane. In this case, only diacetate Ie was isolated. Analogous acetylation of hemiacetal IIa gave acetate IIb. Brief treatment of lactol Ia in benzene containing dihydropyran and *p*-TosOH led to the acetal tetrahydropyranyl ether If. The principal objective, dihydropyran III, was realized by elimination of MeOH from acetal Id using *p*-TosOH. As the prelude to another aspect of this work, conditions for oxidizing ether IVa to lactone IVb were reviewed. Jones' reagent[3] in glacial HOAc at 60° proved superior to Na dichromate in the same solvent.

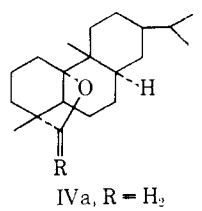


Ia, R = R_1 = H
b, R = CH_3; R_1 = H
c, R = CH_3; R_1 = SO_2CH_3
d, R = CH_3; R = $COCH_3$
e, R = R_1 = $COCH_3$
f, R = R_1 =

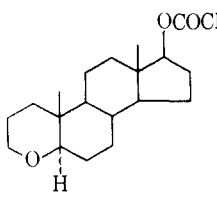
IIa, R = H
b, R = $COCH_3$



III



IVa, R = H_2
b, R = O



V

Each of the 4-oxasteroids was submitted to the Cancer Chemotherapy National Service Center for endocrinological study. The most significant aspect of biological results presently available is that both dihydropyran III and the corresponding tetrahydropyran V[2a,b] were found inactive in an evaluation for androgenic and myogenic activity. The bioassay was conducted with the weanling age rat and compound administered (sc in steriod-suspending vehicle) once each day (10 total). Potency of the steroid as compared with a standard androgen was measured by the change in weight of the levator ani, seminal vesicle, and ventral prostate.

Experimental Section

THF, dihydropyran (both from Na), and all other solvents were redistilled. Acetylation reactions were performed employing 1:4 Ac_2O–pyridine. Solvent extracts of aq soln were dried (Na_2SO_4). Activated alumina refers to Merck (Rahway) "Suitable for Chromatography."

Pmr ($CDCl_3$, Me_4Si, Varian A-60) spectra were recorded by P. A. Whitehouse and R. P. Panziea (Arizona State University). The pmr data was consistent with the structure assigned each new compound. Element analyses were provided by Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ± 0.4% of the theoretical values.

3ζ-Methoxy-17β-methylsulfonyloxy-4-oxa-5α-androstane (Ic).—In a typical experiment hemiacetal Ia (0.3 g)[2a] in MeOH (12 ml) containing 2 drops of 48% HBr was allowed to remain at room temp 1 hr. Within 10 min acetal Ib began to cryst from soln, yield 0.28 g. Recrystallization from MeOH gave needles weighing 0.22 g, mp 215–217°. Another 0.05-g sample melting at 214–216° was recovered from the mother liquor. The (1:1 EtOAc–$CHCl_3$ mobile phase) indicated a mixture of C-3 epimers. To a soln of acetal Ib (0.62 g) in dry C_6H_6 (10 ml)–dry C_5H_5N (2.5 ml) at ice-bath temp was added $MeSO_2Cl$ (0.3 g) in C_6H_6 (2 ml). The halide was added during 5 min and stirring with cooling continued 2 hr. Solvent was removed *in vacuo* at room temp and the residue treated with ice H_2O and 6 *N* HCl (10 ml). Solid was collected, washed with H_2O, and dissolved in $CHCl_3$ and the soln washed successively with H_2O, 6 *N* HCl, and H_2O. The residue obtained upon removal of solvent was chromatographed in 1:1 hexane–C_6H_6 on activated alumina (10 g). Elution with the same solvent gave 0.25 g of viscous oil. Trituration with Et_2O afforded a solid which crystd from CH_2Cl_2–Et_2O as needles, mp 156–158°. Recrystallization from the same solvent did not change the melting point. In another experiment 0.5 g of acetal Ib was used and the reaction continued for approx 20 hr. In this case, the 1:1 hexane C_6H_6 fraction yielded 0.3 g of solid. After washing with Et_2O the solid weighed 0.2 g and melted at 154–156°. Recrystallization from CH_2Cl_2–Et_2O gave an analytical specimen as needles melting at 156–158°. *Anal.* ($C_{20}H_{34}SO_5$) C, H.

3ζ-Methoxy-17β-acetoxy-4-oxa-5α-androstane (Id).—Hemiacetal Ia (1.0 g)[2a] was acetylated (overnight at room temp) and the product (1.2 g) was recrystd from MeOH–H_2O to yield needles melting at 134–137°. A pure sample of Me acetal Id recrystd from MeOH–CH_2Cl_2 as plates melting at 143–145°. *Anal.* ($C_{23}H_{34}O_4$) C, H, O.

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(1) For part 62 see: G. R. Pettit, L. H. Houghton, J. C. Knight, and F. Bruschweiler, *J. Org. Chem.*, **34**, 2895 (1970).

(2) (a) G. R. Pettit, A. K. Das Gupta, and U. R. Ghatak, *Steroids*, **1**, 137 (1963). (b) For a stereochemical interpretation of analogous hemiacetals and acetals, refer to G. R. Pettit, J. C. Knight, and W. J. Evers, *Can. J. Chem.*, **44**, 807 (1966).

(3) K. Bowden, I. M. Heilborn, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

3ζ,17β-Diacetoxy-4-oxa-5α-androstane (Ie).—Acetylation of hemiacetal Ia (0.4 g) was repeated (see Id). In this case the crude product weighed 0.45 g and melted at 120–122°. Recrystn from Me_2CO–pentane gave needles melting at 141–144°. Further recrystn from the same solvent provided an analytical sample of diacetate Ie, mp 142–144°. *Anal.* ($C_{22}H_{34}O_5$) C, H, O.

Comparison of acetal Id, mp 141–143°, with diacetate Ie, mp 141–144°, by mixture melting point determination showed a depression to 115°.

17β-Acetoxy-4-oxa-2-androstene (III).—A soln of acetal Id (0.2 g) in C_6H_6 (25 ml) containing *p*-TosOH (0.04 g) was heated at reflux 20 hr. The mixture was washed successively with H_2O, aq $NaHCO_3$, and H_2O. Following removal of solvent, the residue was chromatographed on activated alumina. Elution with 1:1 hexane–C_6H_6 led to 0.14 g of III. The oily product crystd from MeOH as small needles melting at 118–120°. Recrystallization from MeOH gave a pure sample, mp 120–121°. *Anal.* ($C_{20}H_{30}O_3$) C, H, O.

Formation of III was monitored by tlc (1:1 C_6H_6–$CHCl_3$, mobile phase) and extended reaction periods (for example, 66 hr) were shown to yield a series of products.

3ζ,17β-Bis(dihydropyranyloxy)-4-oxa-5α-androstane (If).—A soln prepared from C_6H_6 (12 ml), hemiacetal Ia (0.21 g), dihydropyran (2 ml), and *p*-TosOH (0.05 g) was stirred 1 hr at room temp. The soln was washed with aq $NaHCO_3$ and H_2O. Removal of solvent *in vacuo* gave a semisolid which crystd from MeOH–Me_2CO as small needles weighing 0.10 g, mp 165–169°. Recrystallization from the same solvent afforded thick needle clusters melting at 176–179°. *Anal.* ($C_{28}H_{46}O_5$) C, H, O.

3ζ-Acetoxy-4-oxa-5α-cholestane (IIb).—A sample (0.25 g) of 3ζ-hydroxy-4-oxa-5α-cholestane (IIa)[2b] was acetylated as summarized in the case of Ia (see Ie). The crude acetate crystd from pentane as thick needles melting at 103–107° (sintering at 90°). An anal. sample, recrystd from pentane, melted at 105–108° (sintering at 95°); tlc 1:2 C_6H_6–$CHCl_3$. *Anal.* ($C_{28}H_{48}O_2$)C, H, O.

Oxidation of 12α,15-Epoxy-12-nor-13β-methyl-11β,14α-abietane (IVa). Method A.—A soln of XXIa (0.20 g)[4] in glacial AcOH (6 ml) was treated with a slight excess of an 8 *N* CO_3 reagent[3] at 60°. Heating was continued at steam bath temp for 10 min. Excess oxidizing agent was removed by adding MeOH. Following diln with H_2O and extraction with Et_2O containing $CHCl_3$, the extract was washed well with H_2O, aq $NaHCO_3$, and H_2O. Removal of solvent gave 0.17 g of solid which was chromatographed in pentane on activated alumina. Elution with pentane removed 0.03 g of starting material. A fraction eluted by 1:1 pentane–C_6H_6 provided 0.12 g of dihydroabietic γ-lactone (IVb)[4] melting at 125–127°. Recrystallization from MeOH gave long needles melting at 126–128°.

Method B.—Oxidation of IVa (1.1 g)[3] was repeated in a soln composed of glacial AcOH (16 ml), C_6H_6 (6 ml), and $Na_2Cr_2O_7 \cdot 2H_2O$ (2.1 g).[5] The soln was stirred and maintained at approx 75° for 30 hr. The product was isolated and purified as noted directly above. In this case, 0.87 g of starting ether IVa was recovered and 0.26 g of lactone IVb was isolated.

Acknowledgment.—This investigation was supported by Public Health Service Research Grants CA-04074-06 and CA-10115-01 from the National Cancer Institute.

(4) G. R. Pettit, B. Green, T. R. Kasturi, and U. R. Ghatak, *Tetrahedron*, **18**, 953 (1962).

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Hypocholesteremic Agents. 2. Cyclohexane and Indan Derivatives

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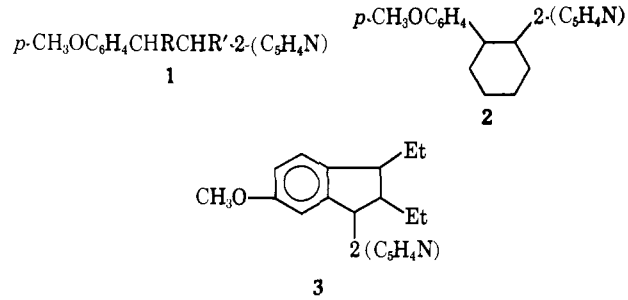
Received May 29, 1970

Maximum hypocholesteremic activity and minimal estrogenic potency was found in the dihydrostilbazole series containing lower alkyl substituents on both carbons of the ethylenic bridge (**1**).[1] It was of interest to study the hypocholesteremic activity of compounds in which R and R[1] are fused in a cyclohexane ring (**2**) or are part of an indan structure (**3**).



Compounds of formulas **2** and **3** were prepared by treating the appropriately substituted cyclic ketone with pyridyllithium, followed by dehydration of the tertiary carbinol and hydrogenation of the resulting double bond. 2-*p*-Methoxyphenyl-1-(2-pyridyl)-1-cyclohexanol having OH on C α to 2-pyridyl, as in the cases previously reported,[1] resisted dehydration by the usual acid dehydrating agents. However, fusion of this carbinol with potassium pyrosulfate gave a mixture of the 1,2- and 2,3-cyclohexenes (**4**).[2,3] The addition of 2-pyridyllithium to **6** gave the tertiary carbinol which was converted into the indene derivative **8a** by heating with H_3PO_4. In contrast, the addition of 3-pyridyllithium to **6** gave the unsaturated compound **8b** directly and provides further evidence for the stability of the 2-pyridyl carbinol moiety.

At the screening dose of 50 mg/kg orally and 10 mg/kg subcutaneously,[4] these compounds were ineffective in lowering the serum cholesterol levels in both male and female rats. The compounds were devoid of estrogenic activity even at higher doses. Previous investigators[5a,b] have shown that 1,2-bis(*p*-methoxyphenyl)cyclohexane has definite but weak estrogenic activity.

Experimental Section[6]

β-Ethyl-*p*-methoxycinnamic Acid.—The Reformatsky ester (160 g), bp 125–155° (1 mm), obtained from 164 g (1 mole) of *p*-methoxypropiophenone, 167 g of ethyl bromoacetate, and 85 g of Zn (20 mesh) was saponified with 160 g of KOH in 1600 ml of EtOH and 800 ml of H_2O to give the trans acid, mp 132–134, and cis acid, mp 68–70°. *Anal.* ($C_{12}H_{14}O_3$) C, H.

β-Ethyl-*p*-methoxyhydrocinnamic Acid (7).—In 4 portions a solution of 84 g of the above acids in 1 l. of EtOH was reduced in a Parr hydrogenator in presence of 20 g of 5% Pd–C. The catalyst was filtered, the solvent removed *in vacuo*, and the residue triturated with pet ether. The product was crystd from hexane: yield 73 g; mp 81–83°. *Anal.* ($C_{12}H_{16}O_3$) C, H.

3-Ethyl-6-methoxyindan-1-one (5).—Acid **7** (35 g) and 1700 g of polyphosphoric acid were heated with stirring on the steam

(1) F. J. Villani, C. A. Ellis, R. F. Tavares, M. Steinberg, and S. Tolksdorf, *J. Med. Chem.*, **13**, 359 (1970).

(2) The mixture was not separated into its components but was used directly in the hydrogenation.

(3) The composition of the mixture was determined by nmr and contained approximately equal amounts of both isomers. We are indebted to Mr. James Morton of the Physical Analytical Department of the Schering Corp. for his interpretations of the nmr spectrum.

(4) The authors are indebted to Drs. S. Tolksdorf and M. Steinberg of the Department of Endocrinology of the Schering Corp. for the biological data.

(5) (a) G. P. Mueller and D. Pickens, *J. Amer. Chem. Soc.*, **72**, 3626 (1950); (b) G. P. Mueller and R. May, *ibid.*, **71**, 3313 (1949).

(6) Melting point are uncorrected and were obtained on a Thomas Hoover open capillary melting point apparatus. Where analyses are indicated only by the symbols of the elements, analytical values are within 0.4% of the theoretical values.

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