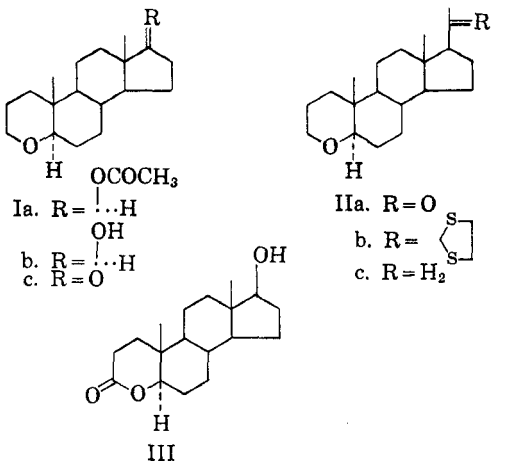
Steroids and Related Natural Products. III. 4-Oxasteroids[1,2]

Sir:

Recently, two potentially useful methods for the synthesis of difficultly accessible oxasteroids were reported.[3] For example, the reaction between 3β,17β-diacetoxy-6β-hydroxy-5α-androstane and lead tetraacetate was shown to provide 3β,17β-diacetoxy-6,19-epoxy-5α-androstane[4]; while boron trifluoride-lithium aluminum hydride reduction of 3β-hydroxy-17-oxo-17a-oxa-D-homo-5α-androstane was found to yield 3β-hydroxy-17a-oxa-D-homo-5α-androstane.[1] We now wish to present facile syntheses for 17β-hydroxy-4-oxa-5α-androstane (Ib), 4-oxa-20-oxo-5α-pregnane (IIa) and several related substances, based on the one-step ester → ether reaction.[1] We also wish to present structural and stereochemical assignments for the ring-A lactones arising from persulfate oxidation of testosterone propionate and progesterone.

Ozonolysis of testosterone propionate, followed by sodium borohydride reduction of the product, gave lactone III.[5] Persulfuric acid oxidation of testosterone propionate, in acetic acid solution, and subsequent base hydrolysis, afforded the same 5α-lactone (III); m.p. 177–179°, $[\alpha]_D^{22}$ +91.7° (chloroform). Boron trifluoride-lithium aluminum hydride reduction of lactone III (0.52 g.) followed by acetylation (acetic anhydride-pyridine) yielded 17β-acetoxy-4-oxa-5α-androstane (Ia, 0.26 g.); colorless rods, m.p. 104–105°, $[\alpha]_D^{22}$ +42.8° (chloroform). *Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; O, 14.98. Found: C, 74.91; H, 9.94; O, 15.18. The 17β-hydroxy derivative Ib recrystallized from aqueous methanol as colorless needles, m.p. 204–206°, $[\alpha]_D^{22}$ +43.8° (chloroform). *Anal.* Calcd. for $C_{18}H_{30}O_2$: C, 77.71; H, 10.79; active H, 0.36. Found: C, 77.21; H, 10.70; active H, 0.40. Treating an acetone solution of alcohol Ib (0.1 g.) with 8*N* chromic acid[6] gave 4-oxa-17-oxo-5α-androstane (Ic, 0.06 g.); colorless needles, m.p. 117–119°, $[\alpha]_D^{22}$ +114.5° (chloroform). *Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; O, 11.58. Found: C, 78.08; H, 10.24; O, 11.63.



III

Progesterone was oxidized to 4-oxa-5α-pregnane-3,20-dione using potassium persulfate.[7] Reducing the lactone (0.79 g.) in tetrahydrofuran solution with boron trifluoride-lithium aluminum hydride and chromic acid[6] oxidation of the resulting mixture led to 4-oxa-20-oxo-5α-pregnane (IIa, 0.54 g.); colorless plates from *n*-hexane, m.p. 144–145°, $[\alpha]_D^{22}$ +125.8° (chloroform). *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51. Found: C, 78.82; H, 10.52; O, 10.65. Raney nickel desulfurization of the ethylenethioketal derivative IIb (0.15 g.), m.p. 202–203°, (*Anal.* Calcd. for $C_{22}H_{36}OS_2$: C, 69.44; H, 9.54; S, 16.82. Found: C, 69.10; H, 9.51; S, 16.39.) gave 4-oxa-5α-pregnane (IIc, 0.085 g.); colorless plates from methanol, m.p. 107–108°, $[\alpha]_D$ +56.0° (chloroform). *Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.35; H, 11.57. Baeyer-Villiger oxidation of ketone IIa (0.5 g.) to 17β-acetoxy-4-oxa-5α-androstane (Ia, 0.45 g.), with trifluoroperacetic acid, supported the structures and stereochemistry assigned compounds IIa-c.

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(1) Part II, G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, 25, 875 (1960).

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(3) See G. V. Bhide, N. L. Tikotkar, and B. D. Tilak, *Tetrahedron*, 10, 223 (1960); J. T. Edward and P. F. Morand, *Can. J. Chem.*, 38, 1325 (1960); and a recent review by B. D. Tilak, *J. Indian Chem. Soc.*, 36, 509 (1959), for a summary of previous synthetic approaches to oxygen heterocyclic steroids.

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