

in an ice bath, 200 ml of Me₂CO was added and 4.5 ml (12% excess) of CrO₃ reagent (8 N in 8 N H₂SO₄)^{15,16} was added with stirring. The reaction mixture was poured onto ice and diluted with H₂O to give 5.53 g of **5** mp 254.5–259.5°. Anal. C, H, N.

Ammonium 17-Keto-3-methoxyestra-1,3,5(10)-trien-2-yl-sulfonate (8).—Estrone methyl ether (10.5 g) was dissolved in 50 ml of boiling C₆H₆, 10 ml was distilled, and the solution was then cooled in an ice bath with stirring until precipitation began. Then 4.3 ml (2.4 equiv) of ClSO₃H was added over ca. 10 min (addition after the first equiv was accompanied by formation of a solid). The reaction mixture was stirred for another 30 min, was poured onto 120 ml of concentrated NH₄OH and the mixture was triturated and evaporated to dryness. The solid was triturated and washed with H₂O, mp 290–300° dec. Samples which were dissolved in NaHCO₃ or NaOH did not reprecipitate on acidification. The solid was triturated with CHCl₃, filtered, and dried to give 12.2 g, mp >280° dec; ir identical with that of nitrated material. The solid was soluble in hot H₂O and its solution gave NH₃ (odor and moist alkacid paper) on addition of base; ir as expected. Anal. C, H, N, S.

17 α -Ethynyl-3-methoxy-2-sulfamyl-estra-1,3,5(10)-trien-17 β -ol (7).—3-Methoxy-2-sulfamylestra-1,3,5(10)-trien-17-one (4.56 g) in 100 ml of THF was added dropwise at 5–10° over 50 min under N₂ to a stirred suspension of 12 g of lithium acetylide ethylenediamine complex in 50 ml of THF. After 5.5 hr, H₂O was added dropwise to quench the reaction; it was further diluted and acidified with H₂SO₄. At this point an oil separated. The pH was adjusted to ca. 8 with 10% NaHCO₃ (200–300 ml) and the mixture was cooled overnight. The oil solidified and the solid was collected; 4.07 g, mp 207–217°. Attempted purification by recrystallization from MeOH gave 1.05 g, mp 218.5–247°, and dilution of the filtrate with H₂O gave 2.33 g, mp 194.5–208°. Both contained significant amounts of the ketone (ir); the solids were combined and chromatographed over silica gel in C₆H₆-EtOAc (10–100%). A peak eluted with 20% EtOAc was dissolved in *i*-PrOH and 25 ml of EtOH, 10 ml of HOAc, and 1.0 g of Girard's reagent T were added to remove unreacted ketone.¹⁷ After boiling for 1 hr, the solution was poured onto ice, diluted with H₂O, and filtered to give 1.84 g, mp 210.5–220°. A further recrystallization from *i*-PrOH gave 560 mg of **7** after washing with Et₂O and drying; mp 219–228° (viscous melt); ir as expected; pmr as expected for methyls, ethynyl, isolated aromatic H, OH, and CONH (the last two eliminated by D₂O exchange). Anal. C, H, N.

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Thia Steroids. II.

2-Thia-A-nor-5 α -pregnan-20-one¹

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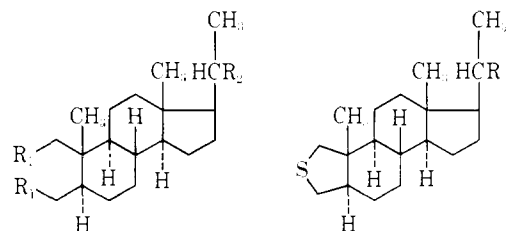
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In view of the androgenic activity of 2-thia-A-nor-5 α -androstan-17 β -ol² the preparation of a progesterone analog was undertaken by a similar reaction sequence (1–6) as described in the Experimental Section. Com-

(1) This investigation was supported in part by a Public Health Service Research Grant (AM-05016) from the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service.

(2) M. E. Wolff, and G. Zanati, *J. Med. Chem.*, **12**, 629 (1969).



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|---|---------------|
| 1. R ₁ = COOH; R ₂ = 20-Oxo | 5. R = OH |
| 2. R ₁ = COOH; R ₂ = OH | 6. R = 20-Oxo |
| 3. R ₁ = COOH; R ₂ = Ac | |
| 4. R ₁ = Br; R ₂ = Ac | |

pound **6** was inactive as a progestogen in the Clauberg-type test.³

Experimental Section⁴

20-Oxo-2,3-seco-5 α -pregnane-2,3-dioic Acid (1).—To a solution of 5 g of 5 α -pregnan-3,20-dione⁵ in 200 ml of glacial HOAc was added 5 g of CrO₃ at 24° and, the mixture was kept for 5 hr. H₂O was added and the pptd product was collected. It was purified by dissolving in Na₂CO₃ solution and extracting the non-acidic material with Et₂O. The alkaline layer was acidified with dil HCl and the pptd product was crystd from CH₃CN, mp 201–202°, M⁺ = 364. Anal. (C₂₁H₃₂O₅) C, H.

2 β -Hydroxy-2,3-seco-5 α -pregnane-2,3-dioic Acid (2).—To a solution of 4 g of **1** in 250 ml of anhyd THF was added 8 g of LiAl (*t*-BuO)₃H and the mixture was heated under reflux for 1 hr. After removal of the solvent under vacuum, H₂O was added and the product was extd with Et₂O. The Et₂O layer was washed with H₂O, dried (Na₂SO₄), and evapd. Recrystu of the product from MeCN gave crystals, mp 273–275°; M⁺ = 366. Anal. (C₂₁H₃₄O₅) C, H.

2 β -Hydroxy-2,3-seco-5 α -pregnane-2,3-dioic Acid Acetate (3).—A mixture of 10 ml of C₃H₇N, 8 ml of Ac₂O, and 1.2 g of **2** was kept at 24° for 18 hr. The product was isolated with CHCl₃ to afford 1.2 g of **3**; mp 184–185°, after several recrystns from hexane-Me₂CO. Anal. (C₂₃H₃₆O₆) C, H.

1,4-Dibromo-1,4-seco-2,3-bisnor-5 α -pregnan-20 β -ol Acetate (4).—To 1.2 g of **3** in 100 ml of stirred, refluxing CCl₄, there was added 1 g of red HgO. The reaction mixture was shielded from light, and 1 g of Br₂ was added dropwise. After 3 hr the reaction mixture was allowed to cool and the dark mixture was filtered. The filtrate was concd under vacuum and the residue was chromatographed on Al₂O₃ to give 0.6 g of pure **4**, mp 149–150° after recrystu from MeOH; M - 60 = 418. Anal. (C₂₁H₃₄Br₂O₂) C, H.

2-Thia-A-nor-5 α -pregnan-20 β -ol (5).—To a refluxing solution of 0.5 g of **4** in 80 ml of refluxing EtOH, there was added a tenfold excess of Na₂S dissolved in the minimum amount of H₂O. Heating was continued for 20 hr when tlc indicated complete conversion into **5**. The solvent was removed under vacuum and the residue was taken up in Et₂O, washed with dil HCl solution and then H₂O, dried (Na₂SO₄), and evapd to give 0.28 g of **5** as a white solid, which after recrystu from Me₂CO-hexane had mp 193–195°; M⁺ = 308. Anal. (C₁₅H₂₂OS) C, H, S.

2-Thia-A-nor-5 α -pregnan-20-one (6).—A solution of 0.15 g of **5** in 5 ml of cyclohexanone and 0.3 g of Al(*i*-PrO)₃ in 300 ml of PhMe was heated under reflux for 2 hr, cooled, and diluted with H₂O. Steam distn gave an aq suspension which was extd with Et₂O. Removal of the Et₂O under vacuum gave a residue which was adsorbed on silica gel. Elution with 2% EtOAc in C₆H₆ gave the product, which was recrystd from hexane-Me₂CO to give the analytical sample mp 158–159°; M⁺ = 306. Anal. (C₁₅H₂₀OS) C, H.

(3) M. E. Wolff, W. Ho, and M. Honjoh, *ibid.*, **11**, 285 (1968).

(4) Melting points were determined with a Thomas-Hoover apparatus equipped with a corrected thermometer. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley, Calif. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within $\pm 0.4\%$ of the theoretical values.

(5) Purchased from Searle Chemicals, Inc., Lot V-4.