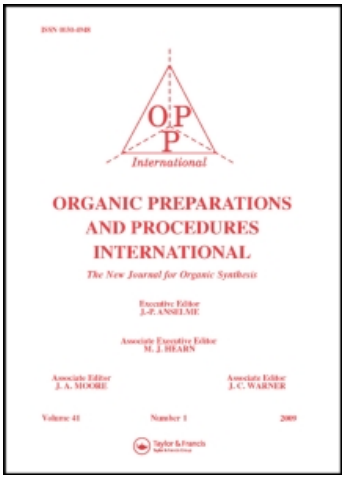

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IMPROVED PREPARATION OF WHYDROXYPROGESTERONE

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IMPROVED PREPARATION OF 18-HYDROXYPROGESTERONE

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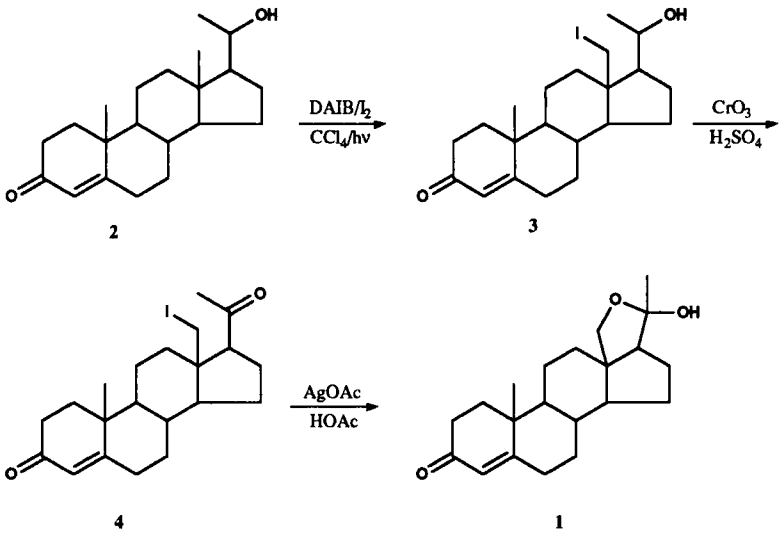
Previous methods used for the preparation of 18-hydroxyprogesterone hemiacetal (**1**) involved multi-step procedures (usually five to seven) and gave low yields of the desired product.[1] Slaunwhite and Solo[1] obtained a 19% yield of **1** in five steps starting from pregnenolone acetate, this being the best yield described in the literature. All these procedures, which involve either the hypoiodite reaction ($Pb(OAc)_4/I_2$) or the Barton reaction (photolysis of a C-20 nitrite) for functionalization of the C-18 angular methyl group, limit the functional groups that may be present in the precursor molecule.

This limitation precludes carrying out a more direct approach, for example, from commercially available 20β-hydroxypregn-4-en-3-one (**2**). In this case the main problem is the chemical instability of the 4-en-3-one grouping in ring A to the hypoiodite and Barton reactions.

Concepción *et al.* introduced the use of the hypervalent iodine compound diacetoxyiodobenzene (DAIB), for remote iodination of non-activated carbons in a hypoiodite type



reaction.[2] Good yields were reported for the preparation of an 18-iodosteroid using DAIB/iodine in cyclohexane under photochemical conditions. In our hands, the DAIB/iodine system when applied to different 20-hydroxysteroids gave good yields of the corresponding 18-iodo derivatives only when the solvent was replaced by freshly distilled carbon tetrachloride. The mildness of the reagent was evidenced upon reaction with 20β-hydroxypregn-4-en-3-one (**2**) which was smoothly converted into the 18-iodo derivative **3**. Oxidation of the latter compound with Jones reagent provided 18-iodoprogesterone (**4**). Conversion of 18-iodoprogesterone into 18-hydroxyprogesterone hemiacetal (**1**) was accomplished using silver acetate in aqueous acetic acid (0 2% water),[3] a procedure which gave consistently higher yields than silver acetate in aqueous dioxane, aqueous acetone or methanol by avoiding the formation of secondary products.[4,5] The overall yield of pure 18-hydroxyprogesterone was 35%.

EXPERIMENTAL SECTION

Mps were measured on a Fisher Johns apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were measured in a Varian XL-100-15 FT NMR spectrometer at 100.1 MHz; chemical shifts are given in ppm downfield from internal TMS. Mass spectra were measured by EI at 70 eV by direct inlet. Diacetoxyiodobenzene was purchased from Aldrich. 20β-Hydroxypregn-4-en-3-one (**2**) was purchased from Sigma. All solvents used were reagent grade.

NOTE: CCl_4 is a carcinogen; handle with care.

18-Iodoprogesterone (4).- To a solution of 20β-hydroxypregn-4-en-3-one (**2**) (250 mg) in freshly distilled CCl_4 (70 mL) was added diacetoxyiodobenzene (290 mg) and iodine (200 mg). The mixture was vigorously stirred under irradiation with a 300 Watt tungsten lamp (5000 lumens) for 70 min at 25°. The resulting solution was poured into 5% sodium thiosulfate and extracted with ether, then washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded an oily residue (400 mg) containing 18-iodo-20β-hydroxypregn-4-en-3-one (**3**) and iodobenzene. The crude product was dissolved in acetone (130 mL), O_2-free nitrogen was bubbled through the solution for 30 min and the solution cooled to 0° and Jones reagent (0.36 mL) added dropwise. After 20 min the excess oxidant was destroyed with 2-propanol and the reaction mixture diluted with water. Extractive workup afforded an oily residue which was percolated through Florisil eluting with hexanes (100 mL) and then ethyl acetate (100 mL). Evaporation of the latter fraction, afforded 18-iodoprogesterone (**4**) (250 mg, 71%) which was used in the following step without further purification. An analytical sample purified by preparative tlc (hexanes-ethyl acetate 1:1) had mp. (methanol-H_2O) 102-105° (dec.), lit.[4] 103-104°. ^{1}H NMR: δ 1.20 (s, 3H, H-19), 2.29 (s, 3H, H-21), 3.21 (s, 2H, H-18), 5.85 (s, 1H, H-4). MS (EI), *m/z* (rel. %): 312 $[M\text{-}HI]^+$ (8), 294 $[312\text{-}H_2O]^+$ (8).

18-Hydroxyprogesterone Hemiacetal (1).- 18-Iodoprogesterone (**4**) (250 mg) was dissolved in glacial acetic acid containing 0.2% water (5 mL) and silver acetate (170 mg) added. The reaction mixture was stirred for 90 min at 55° in the dark, filtered, diluted with water and neutralized with solid $NaHCO_3$. Extractive workup with CH_2Cl_2 followed by column chromatography (Florisil, hexanes-ethyl acetate mixtures of increasing polarity) afforded pure 18-hydroxyprogesterone hemiacetal (**1**) (90 mg), mp. 157-159° (acetone), lit.[6,5] 157-159°, 153-156°. ^{1}H NMR: δ 1.14 (s, 3H, H-19), 1.48 (s, 3H, H-21), 3.75 (s, 2H, H-18), 5.85 (s, 1H, H-4). MS (EI), *m/z* (rel. %): 312 $[M\text{-}H_2O]^+$ (100), 270 $[312\text{-}CH_2CO]^+$ (18).

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