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# PRELIMINARY NOTE

## SYNTHESIS OF 19-IODO-5-ANDROSTENE-3β, 17β-DIOL-17β-YL-ACETATE

HARRY E. HADD
Department of Biochemistry, Northwest Center for Medical Education,
Indiana University School of Medicine, 3400 Broadway,
Gary, IN 46408, U.S.A.

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SUMMARY

19-Iodo-5-androstene-3β, 17β-diol-17β-yl-acetate was synthesized from 19-acetoxy-5-androsten-17-one in 1.6% overall yield.

### INTRODUCTION

We required several 19-iodo-steroids in the androgen series for our biological testing program on possible prostate imaging agents [1]. Reported here is the sequence leading to 19-iodo-5-androstene-3β, 17β-diol-17β-yl-acetate. The specific insertion of the 19-iodo group was patterned from the general procedure of *p*-toluenesulfonyl-oxy-displacement by halide ion, a method employed by others to obtain 19-chloro-17β-hydroxy-4-androsten-3-one [2, 3], 19-bromo-5-androsten-17-one [4], and 19-iodo-5-cholesten-3β-ol [5, 6]. Counsell and associates [6] converted the latter compound to its radio-iodinated analogue, of unique importance as an adrenal imaging agent [7].

### METHODS AND RESULTS

The 3β, 19-dihydroxy-5-androsten-17-one (**I**) was diacetylated to yield 3β, 19-diacetoxy-5-androsten-17-one (**II**), m.p. 107–109 C (lit. 109–110 C [8]); i.r. 1735 $cm^{-1}$ (broad), 1250 $cm^{-1}$; n.m.r. (ppm), 19-$CH_2$ 4.56, 3.96 ($J$ = 12); elemental analysis, calc. for $C_{23}H_{32}O_5$, C 71.11, H 8.30, found C 71.11, H 8.29. **II** was selectively 3-deacetylated by $KHCO_3$ in methanol [9] to yield **III**, 19-acetoxy-3β-hydroxy-5-androsten-17-one, m.p. 126.5–127.5 C (lit. 123–124 C [9]); i.r.-OH stretch (broad) 3500 $cm^{-1}$, C=O 1735 $cm^{-1}$; n.m.r. (ppm), 19-$CH_2$, 4.51, 3.94 ($J$ = 12); calc. for $C_{21}H_{30}O_4$, C 72.80, H 8.73, found 72.75, H 8.79. Treatment of **III** with dihydropyran [9–11] yielded **IV**, the 3β-(2-tetrahydropyranyl)-oxy-derivative, m.p. 114–121 C; i.r. C=O 1740 $cm^{-1}$; n.m.r. (ppm), 19-$CH_2$, 4.54, 3.95 ($J$ = 13); calc. for $C_{26}H_{38}O_5 . C_2H_5OH$, C 70.6, H 9.3, found C 70.0, H 8.8. Removal of the 19-acetyl group of **IV** by NaOH in 95% ethanol gave **V**, 19-hydroxy-3β-(2-tetrahydropyranyl)-oxy-5-androstene-17-one, m.p. 177–180 C; i.r. 3500 $cm^{-1}$; n.m.r. (ppm), 19-$CH_2$, 3.89, 3.62 ($J$ = 13); calc. for $C_{24}H_{36}O_4$, C 74.2, H 9.3, found C 72.8, H 9.2. Reaction of **V** with methanesulfonyl chloride in pyridine [12] yielded 19-methanesulfonyl-oxy-3β-(2-tetrahydropyranyl)-oxy-5-androsten-17-one, **VI**, m.p. 126–129 C; i.r., absent —OH stretch 3450 $cm^{-1}$; n.m.r. (ppm), 19-$CH_2$, 4.46, 4.17 ($J$ = 11); calc. for $C_{25}H_{38}O_6S$, C 64.35, H 8.21, S 6.87, found C 64.28, H 8.22, S 7.02. Treatment of **VI** with $NaBH_4$ [13] gave the 17β-ol derivative, **VII**, m.p. 121.5–122.5 C; i.r., —OH stretch 3450 $cm^{-1}$, absent 17-C=O 1740 $cm^{-1}$; n.m.r. (ppm), 19-$CH_2$, 4.44, 4.17 ($J$ = 11). Acetylation of **VII** yielded the 17β-yl-acetate, **VIII**, m.p. 116.5–118.5 C; i.r. absent —OH stretch 3450 $cm^{-1}$, presence of C=O 1730 $cm^{-1}$; n.m.r. (ppm), 19-$CH_2$, 4.44, 4.15 ($J$ = 11). Displacement of 19-methanesulfonyl-oxy from **VIII** by LiI [4] in refluxing isopropanol gave 19-iodo-3β-hydroxy-5-androsten 17β-yl-acetate, **IX**, m.p. 145–146 C; i.r., sharp —OH stretch 3400 $cm^{-1}$, C=O 1715 $cm^{-1}$; n.m.r. (ppm), 19-$CH_2$, 3.57, 3.25 ($J$ = 12); mass spectra, small molecular ion 458, 457, 332, 331 (princ. ion), 330, 313, 312 (large), 298, 297, 289, 271, 252, HI 128, I 127; calc. for $C_{21}H_{31}IO_3$, C 55.03, H 6.82, I 27.69, found C 55.23, H 6.73, I 27.58. Overall yield of **IX** from **I** was 1.6%, with an average yield of 65% at each step.

### DISCUSSION

The n.m.r. spectral pattern arising from the 19-$CH_2X$-**AB** system in the compounds in the synthetic sequence was of interest. The chemical shift of the **AB** pattern of the 19-$CH_2X$ was dependent upon the deshielding nature of X, the protonic signals being further downfield for mesyl-oxy 4.32 ppm, and diminishing to 4.26 acetoxyl, to 3.76 ppm for hydroxyl, and to 3.41 ppm for iodo. It was observed that the chemical shift values of the 19-$CH_2$ group was a function of the electron withdrawing function of the substituent and independent of the nucleus, androstene or cholestene. The difference in protonic chemical shift values between the —$CH_2$— of 19-mesyloxy- and 19-iodo- was 90 Herz, which was the largest difference of chemical shift values observed between starting material and its product. Mass spectra of the 19-iodo compound showed the molecular ion 453, and the fragments resulting from the loss of $I^-$ and HI, 332 and 331, the latter being the principal ion. There followed predicted fragments with loss of $H_2O$ (18), $CH_3COOH$ (60). There was observed the 127 and 128 of $I^-$ and HI, indicating the presence of the iodo group. Elemental Analysis for the product was satisfactory and confirmed iodo group presence.

The biological activity of the 19-iodo steroid and others in this series will be published separately [14].

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