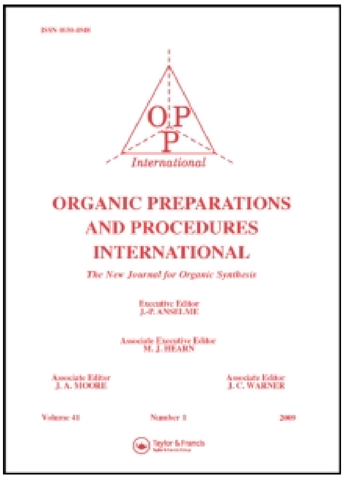

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KETALIZATION OF 5-KETO STEROID ESTERS[1]

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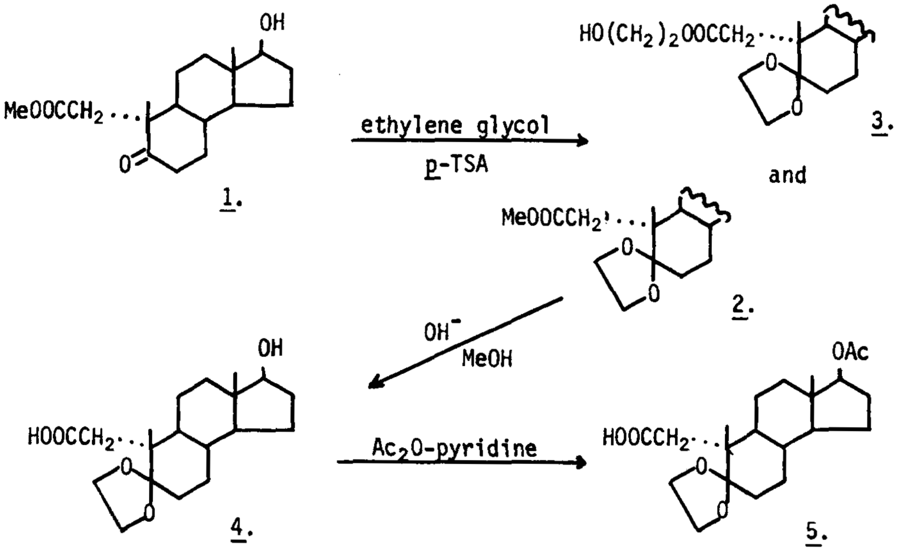

Our investigations on heterocyclic steroids[3] required the preparation of a 2,3,4-trisnorsteroid having a 19-methyl group. Therefore, a degradation of testosterone similar to our work[4] with 19-nortestosterone was begun.[5]

We now report the preparation of a number of new compounds which were used in the initial stages of this sequence. Our experience with the ketalization reaction indicated it to be quite facile for the formation of ketal 2, but transesterification of the ester moiety with ethylene glycol yielding ester 3 was observed as a significant side reaction. Saponification of the methyl ester 2 was found to require a longer than usual reaction time to give acid 4, which was acetylated to acetyl acid 5.

EXPERIMENTAL[6]

Ketalization of Ketoester 1. A mixture of 100 mg of ketoester[7] 1, 20 mg of p-toluenesulfonic acid (p-TSA), 2.0 ml of ethylene glycol, and 50 ml of dry benzene was heated to reflux for 16 hr. The water formed during the reaction was collected in a Dean-Stark tube.[8] The reaction mixture was cooled, and solid Na_2HCO_3 was added. The benzene solution was then diluted with ether and washed with water. Evaporation of the solution (dried over Na_2SO_4) yielded 110 mg of crude material which was chromatographed on a silica gel TLC plate[9] with 40% ethyl acetate-chloroform. Repeated recrystallization of the chromatographically pure material 2 (85 mg; 74.5%) from ethyl acetate-pentane gave an analytical sample; mp. 129-131^o; ν_{max} 3540, 1720 cm^{-1}; nmr. 45.5 (18 Me), 68.5 (19 Me), 140.5 (doublet; J=2.0; C-1 protons), 224 (Me of ester), and 240.5 cps (doublet; J=1.0; ketal protons).

Anal. Calcd. for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.24; H, 9.02.

A larger run with 1.62 g of ketoester 1, 100 mg of p-TSA, 30 ml of glycol, and 300 ml of benzene gave 2.0 g of crude material. Recrystallization from ethyl acetate gave about 300 mg (12.1%) of ester 3. A TLC analysis of the mother liquor indicated that it consisted essentially of ketal 2. Concentration of the mother liquor later produced 1.1 g (48%) of ketal 2.

Repeated recrystallization of ester 3 from acetone gave a pure sample; mp. 163-166°; ν_{max} 3370, 1725 cm^{-1}; nmr. 44.5 (18 Me), 66.0 (19 Me), 137.5 (C-1 protons), 234.5 cps (W_h=about 3 cps; ketal protons).

Anal. Calcd. for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96. Found: C, 66.01; H, 9.06.

Acid 4. A solution of 1.06 g of ester 2 and 30 ml of 2N NaOH in 50 ml of methanol was refluxed for 18 hr. The solution was diluted with water and extracted with ether to remove the starting material. Acidification of the aqueous phase at 0° followed by crystallization of the acid from ethyl acetate gave 784 mg (77%) of acid 4. This crystalline material was further purified by repeated recrystallizations (from methylene chloride-ethyl acetate); mp. 175-180° (with sintering); ν_{max} 3380, 1700 cm^{-1}.

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.38; H, 8.80.

Acetylated Acid 5. Acid 4 (100 mg) was acetylated with acetic anhydride in pyridine[10] to give 98 mg (87%) of acetate 5. Recrystallization from ethyl acetate yielded a sample; mp. 198°; ν_{max} 1730, 1685 cm^{-1}.

Anal. Calcd. for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.32; H, 8.37.

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2. Recipient of USPHS Research Career Program Award CA-K3-16614 from the National Cancer Institute.

3. See D. M. Piatak and E. Caspi, J. Heterocyclic Chem., 4, 8 (1967) for leading references.

4. a) E. Caspi, P. K. Grover, D. M. Piatak, and Y. Shimizu, J. Chem. Soc. 3052 (1965); b) E. Caspi and D. M. Piatak, Experientia, 19, 465 (1963).

5. Later studies [D. M. Piatak, H. B. Bhat, and E. Caspi, J. Org. Chem., 34, 112 (1969)] with 1-dehydrotestosterone and ruthenium tetroxide provided a more convenient route to the trisnorsteroid, and the degradation was set aside.

6. Melting points were taken on a hot stage and are corrected. Infrared spectra were recorded on KBr discs with a Perkin-Elmer 237 instrument and nmr. spectra, on $CDCl_3$ solutions with a Varian HA-60 spectrometer.

7. F. L. Weisenborn, D. C. Remy, and T. C. Jacobs, J. Amer. Chem. Soc., 76, 552 (1954).

8. The Dean-Stark tube used was modified by using an outer water-cooled jacket and a long narrow funnel which carried the condensate directly to the bottom of the tube before it was returned to the reaction. In other ketalizations we found thse modifications generally gave optimum yields.

9. The material was detected on the preparative TLC plate by a comparison of the translucent and opaque areas produced by a strong light under the plate with the spots produced by iodine vapors on a separate chromatography of a small amount of the material.

10. E. Caspi and D. M. Piatak, J. Org. Chem., 29, 2948 (1964).

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