[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

4-Aza-17α-methyl-17β-hydroxyandrost-5-en-3-one and Methyltestosterone-4-C^{14} [1,2]

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The synthesis of the title compounds, using methyltestosterone as starting material is described.

It has been shown in a preliminary communication[3] that the attack of ammonia at room temperature on the corresponding keto acids and enol lactones constitutes an easy access to 4-azasteroids. The present paper described the synthesis of 17α-methyl-17β-hydroxy-4-aza-androst-5-en-3-one and its 17β-acetate. We have already reported[3] on the synthesis of 17β-hydroxy-4-aza-androst-5-en-3-one and its 17β-acetate which were prepared in a very similar fashion. In addition the synthesis of methyltestosterone-4-C^{14} is described.

Fission of ring A of methyltestosterone (I) with ozone gave in 70% yield the unknown keto acid II, which was lactonized with acetic anhydride and anhydrous sodium acetate, whereby the 17-hydroxyl became acetylated.

For the preparation of 4-aza-17α-methyl-17β-hydroxyandrost-5-en-3-one, dry ammonia was introduced into the benzene solution of the keto acid II, the mixture left overnight and then evaporated to dryness, yielding a crude mixture.[4] To effect cyclization, the residue was dissolved in acetic acid and heated under reflux for two hours. After evaporating off the solvent the product V could be isolated in a 15% yield. A similar procedure was also carried out with the enollactone III, whereby the 4-aza-17α-methyl-17β-acetoxyandrost-5-en-3-one (VI) was obtained in a 50% yield.

The synthesis of methyltestosterone-4-C^{14} (VII) proceeded along well trodden paths.[5] The addition of methylmagnesium iodide-C^{14} to the enol lactone acetate III, followed by hydrolysis and ring closure gave, without isolation of the intermediates, after chromatography methyltestosterone acetate-4-C^{14} (IV) (37% yield on the basis of methyl iodide). Since an attempted hydrolysis of the ester with 1% methanolic potassium hydroxide under reflux did not succeed, the acetate was removed by hydrogenolysis with lithium aluminum hydride, followed by reoxidation of the concomittantly reduced ketone with manganese dioxide which furnished the desired methyltestosterone-4-C^{14}.[6]

EXPERIMENTAL[7]

17α-Methyl-17β-hydroxy-5-keto-3,5-seco-4-norandrostan-3-oic acid (II). A solution of 4.0 g. of methyltestosterone (I) in 75 ml. of 2:1 methylene chloride–ethyl acetate was oxidized by passing through it ozone at −76° until the color of the mixture was blue. Then the solvents were evaporated, the residue dissolved in glacial acetic acid, 5 ml. of 30% hydrogen peroxide added, and the solution left at room temperature overnight. The solvents were then removed *in vacuo*, the residue taken up in ether and extracted with

(1) Presented, in part, before the Division of Medicinal Chemistry, 137th National A.C.S. Meeting, Cleveland, Ohio, April 1960, p. 19N.

(2) This investigation was supported in part by grants from the U.S.P.H. H-5266.

(3) M. Uskoković and Marcel Gut, *Helv. Chim. Acta*, 42, 2258 (1959).

(4) The mixture could possibly consist of the ammonium salt of II, of its amide and of its pseudoamide (compare 3).

(5) Compare A. Murray III and D. H. Williams, *Organic Syntheses with Isotopes*, Interscience Publ., Inc., New York, N. Y., 1958, pp. 1051.

(6) An alternative, namely protection of the ketonic function by the formation of its ethyl enol ether, followed by hydrogenolysis of the acetate with lithium aluminum hydride was explored in model runs. However, the yields were not superior to the one described in the experimental part.

2*N* sodium hydroxide solution. This extract was acidified with concentrated hydrochloric acid and the resulting crystalline precipitates filtered off and dried. On recrystallization from acetone-hexane 2.9 g. of II, m.p. 188–191° was obtained. $[\alpha]_D^{26}$ −11° ± 3° (*c*, 0.769).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.69; H, 9.11.

5-Hydroxy-17β-acetoxy-3,5-seco-4-norandrost-5-en-3-oic 3,5-lactone (III). To the solution of 2.0 g. of II in 100 ml. acetic anhydride, 4 g. of anhydrous sodium acetate was added and the mixture was refluxed for 3 hr. in a nitrogen atmosphere. Then the solvent was evaporated *in vacuo*, the residue extracted with ethyl acetate, the extract washed with water, dried and finally evaporated, yielding, after recrystallization from acetone, 1.6 g. of colorless prisms, m.p. 154–157°. The analytical sample was sublimed at 140° (0.01 mm.) and recrystallized from acetone, m.p. 155–157°; $[\alpha]_D^{26}$ −75° ± 3° (*c*, 1.010).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.86; H, 8.94.

4-Aza-17α-methyl-17β-hydroxyandrost-5-en-3-one (V).[8] Dry ammonia was introduced into a solution of 500 mg. of keto acid II in 400 ml. dioxane for 2 hr. and then the mixture was left overnight at room temperature. After evaporating the solvent *in vacuo* the residue was dissolved in acetic acid and heated under reflux for 2 hr. The solvent was removed *in vacuo*, taken up in methylene chloride, the extract washed several times with 2*N* sodium carbonate solution, dried, and evaporated. From the residue there was obtained, after trituration with ether, 75 mg. V, m.p. 243–245° dec. An analytical sample was prepared by sublimation at 180° (0.01 mm.), whereby enlongated curved prisms melting, after recrystallization from ether, at 253–257° dec. were obtained. $[\alpha]_D^{26}$ −143° ± 3° (*c*, 0.497) and ν_{max} 3430, 1210, 1060 cm.$^{-1}$ (OH group): 3230 and 3120 cm.$^{-1}$ (NH): 1660 cm.$^{-1}$ (—CO—NH). 815 and 843 cm.$^{-1}$ (double bond). ϵ_{234} 11,500.

Anal. Calcd. for $C_{19}H_{29}O_2N$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.21; H, 9.80; N, 4.77.

4-Aza-17α-methyl-17β-acetoxyandrost-5-en-3-one (*VI*) *from* III. Dry ammonia was introduced into the solution of 300 mg. of III in 300 ml. dry benzene during 8 hr. After evaporation of the solvent, the residue was chromatographed on silica gel, whereby the ethyl acetate–benzene 1:3 fraction eluted 280 mg. VI, which was recrystallized from ether, m.p. 237°, transformation from needles to prisms, and finally melting at 258–260° dec. $[\alpha]_D^{26}$ −100° ± 3° (*c*, 1.451). ν_{max} 3090 and 3210 cm.$^{-1}$ (N—H), 1730 and 1260 cm.$^{-1}$ (acetoxy), 1673 cm.$^{-1}$ (—CO—NH—) 840 and 1630 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{21}H_{31}O_3N$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.42; H, 9.08; N, 4.31.

Methyltestosterone acetate-4-C^{14} (IV). To a solution of 2 mmoles of methylmagnesium iodide-C^{14} (2 mC) in 15 ml. of ether and frozen to −20° was added dropwise the solution of 693 mg. (2 mmoles) of III in 75 ml. ether-benzene (1:2). The mixture was allowed to warm up and then stand at room temperature for 2 additional hr. Then the mixture was decomposed with 2*N* hydrochloric acid and the product taken up in benzene. The benzene layer was washed with 2*N* sodium carbonate solution, then with water, dried, and evaporated. The residue was dissolved in 20 ml. of glacial acetic acid, 1.5 ml. of concd. hydrochloric acid added and the mixture kept for 2 days at 25° in nitrogen atmosphere. After removal of the acids *in vacuo* the remaining syrup was dissolved in benzene, washed with 2*N* sodium carbonate solution and with water. The benzene layer was dried, the benzene distilled off, and the residue chromatographed on silica gel. The benzene–ethyl acetate (10:1) fractions gave, after recrystallization from methanol, 249 mg. IV,[9] m.p. 175–177, specific activity 1 mC/mmole. It was shown by mixed melting point and infrared spectrum to be identical with authentic material.

Methyltestosterone-4-C^{14} (VII) *from IV*. To the solution of 600 mg. of lithium aluminum hydride in 50 ml. ether was added dropwise a solution of 345 mg. (1 mC/mmole) of IV in 150 ml. ether and the mixture refluxed for 3 hr. After cooling to 0° the excess hydride was decomposed by adding ethyl acetate dropwise. Then a cold saturated aqueous solution of sodium sulfate was added until the supernatant was clear. The supernatant was decanted, the residue well washed with ethyl acetate and the solution evaporated to dryness. The 331 mg. of crude residue, m.p. 151–162°,[10] was dissolved in 5 ml. chloroform and shaken at room temperature with 3.5 g. of manganese dioxide for 4 hr. The reagent was then removed by filtration and washed with chloroform. After evaporation of the solvent, the residue was chromatographed on silica gel, obtaining thereby 251 mg. VII, m.p. 162–164°, spec. activity 1 mC/mmole. A mixed melting point with an authentic sample of methyltestosterone showed no depression and its infrared spectrum was identical with that of an authentic sample.

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(7) All melting points were taken on a Kofler block. Rotations were taken in a 1-dm. tube in chloroform. Ultraviolet absorption spectra were determined in methanol by means of a Cary model 11 MS spectrophotometer. The infrared spectra were obtained from a pressed potassium bromide pellet taken on a Perkin-Elmer model 12C spectrometer. All chromatographic separations were made on Davison silica gel mesh 60-200. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(8) N. J. Doorenbos and C. L. Huang, Abstract, 138th National A.C.S. Meeting, New York, N. Y., September 1960, p. 23-O. Chien Li Huang, *Synthesis of Azasteroids of Medical Interest*, Ph.D. thesis, Univ. of Maryland, 1960, p. 63, gives m.p. 256.4° dec., $[\alpha]_D$ −120° (chloroform) and λ_{max} 233 mμ.

(9) S. Kuwada and M. Miyasaka, *J. Pharm. Soc. Japan*, **58**, 319 (1958); K. Miescher and W. Klarer, *Helv. Chim. Acta*, **22**, 962 (1939).

(10) S. Bernstein, S. M. Stolar, and M. Heller, *J. Org. Chem.*, **22**, 472 (1957).