4,17α-Dimethyl-4-aza-5α-androstan-17β-ol Acetate and Related Azasteroids

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Abstract □ 4,17α-Dimethyl-4-aza-5-androsten-17β-ol-3-one, 4,17α-dimethyl-4-aza-5α-androstan-17β-ol-3-one, 4,17α-dimethyl-4-aza-5α-androstan-17β-ol, and their corresponding acetate esters were synthesized and compared for antimicrobial activity. 4,17α-Dimethyl-4-aza-5α-androstan-17β-ol acetate exhibited significant activity.

Keyphrases □ Azasteroids—synthesis, antimicrobial activity evaluation □ 4,17α-Dimethyl-4-aza-5α-androstan-17β-ol acetate, related compounds—synthesis, screening as antimicrobial agents □ Antimicrobial agents, potential—synthesis, screening, 4,17α-dimethyl-4-aza-5α-androstan-17β-ol acetate, esters

Antimicrobial activity was found in 4-azacholestanes (1–6), 4-aza-androstanes (7), 4-azapregnanes (7), 17a-aza-D-homoandrostanes (8), and 2-azacholestane and 3-azacholestane (9) lacking hydroxyl substituents, while corresponding 4-aza-androstanes (2, 4, 5, 7), 4-azapregnanes (4, 7), and 17a-aza-D-homoandrostanes (10) with hydroxy substituents possessed very little activity.

The objective of this study was to determine if esterification of these hydroxyl groups would restore antimicrobial activity. A comparison of the antimicrobial properties of 4,17α-dimethyl-4-aza-5α-androstan-17β-ol (III) and its acetate ester (VI) was selected for this study.

4,17α-Dimethyl-4-aza-5-androsten-17β-ol-3-one (I) (11) was hydrogenated to obtain 4,17α-dimethyl-4-aza-5α-androstan-17β-ol-3-one (II) in 91% yield and reduced with lithium aluminum hydride to give 4,17α-dimethyl-4-aza-5α-androstan-17β-ol (III) in 71% yield (Scheme I). Acetate esters IV, V, and VI were prepared by treatment of I, II, and III with acetic anhydride. Attempts to prepare carbamate esters by reaction of I, II, and III with dimethylcarbamyl chloride and phenyl isocyanate were unsuccessful, except for the preparation of the *N*-phenylcarbamate (VIII) of I following a procedure developed for preparing methyltestosterone *N*-phenylcarbamate (VII) from methyltestosterone.

Each of these azasteroids was compared with *N*-methyl-4-aza-5α-cholestane (ND-502) against a representative group of microorganisms previously found useful in screening azasteroids for activity using described procedures (2). VI, the only active compound, is compared with ND-502 in Table I.

Table I—Antimicrobial Activity

Microorganisms	Minimum Inhibitory Concentration of Steroids (2)[a] VI	ND-502
Staphylococcus aureus	—[b]	5
Escherichia coli	—	—
Candida albicans	50	10
Aspergillus niger	5	5

[a] All values are expressed in micrograms per milliliter. [b] Inactive (no inhibition at 100 mcg./ml.).

EXPERIMENTAL[1]

4,17α-Dimethyl-4-aza-5α-androstan-17β-ol-3-one (II)—To a solution of 1.50 g. (4.7 mmoles) of 4,17α-dimethyl-4-aza-5-androsten-17β-ol-3-one (I) (11) in 50 ml. of glacial acetic acid was added 1.0 g. of platinum dioxide. The mixture was hydrogenated at 70° and 60 p.s.i. for 20 hr. The catalyst was filtered, and the solvent was evaporated *in vacuo*. The residue was crystallized from ether, and the resulting white crystals were used without further purification in the next step. The filtrate was concentrated twice, giving a total yield of 1.37 g. (91%), m.p. 210–211°; $\lambda_{max.}^{EtOH}$ no absorption at 235 nm.; $\lambda_{max.}^{CHCl_3}$ no shoulder at 5.96 μ (hence, —C=C— was reduced).

4,17α-Dimethyl-4-aza-5α-androstan-17β-ol (III)—A solution of 2.00 g. (0.006 mole) of 4,17α-dimethyl-4-aza-5α-androstan-17β-ol-3-one (II) in dry tetrahydrofuran was added dropwise to a cooled suspension of 3.0 g. (0.09 mole) of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran under a nitrogen atmosphere. The mixture was allowed to reflux with stirring for 18 hr. The reaction vessel was cooled in an ice bath while moist tetrahydrofuran was added slowly. The mixture was filtered, the inorganic salts were washed with additional tetrahydrofuran, the solvent was removed *in vacuo*, and the residue was crystallized from acetone to yield 1.44 g. (71%) of III; m.p. 154–156°; $\lambda_{max.}^{CHCl_3}$ no absorption at 6.1 μ (hence, C=O was reduced).

4,17α-Dimethyl-4-aza-5-androsten-17β-ol-3-one Acetate (IV)—4,17α-Dimethyl-4-aza-5-androsten-17β-ol-3-one (I) (1.0 g., 0.03 mole) and 10 ml. of acetic anhydride were refluxed for 30 min. The hot mixture was poured into ice water with stirring. Crystals formed rapidly from the original yellow oil. Recrystallization from acetone yielded white crystals, 970 mg. (87%); m.p. 198–199°; $\lambda_{max.}^{CHCl_3}$ 5.8 and 6.1 μ.

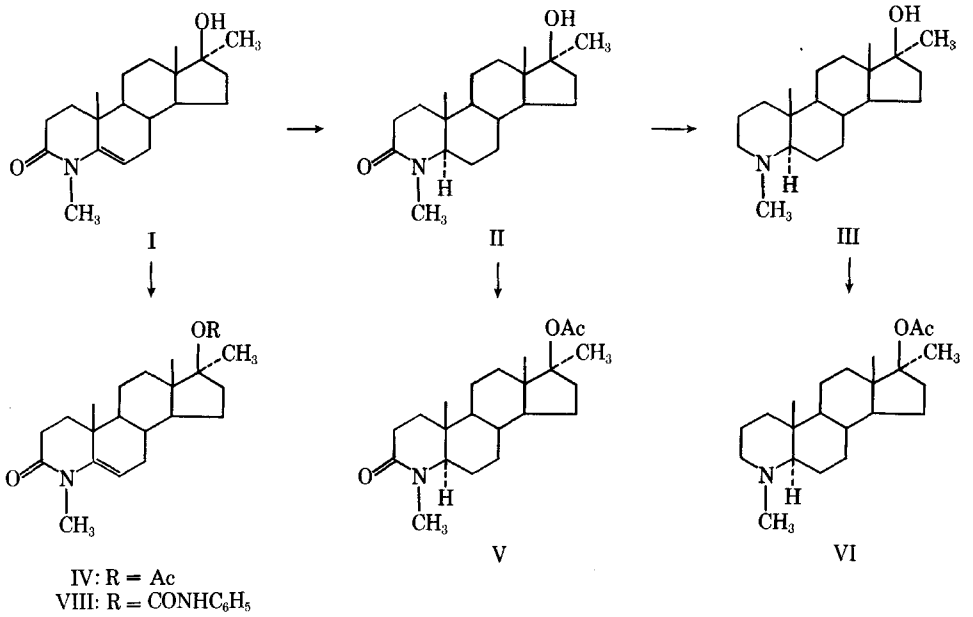
Anal.—Calc. for $C_{22}H_{31}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.90; H, 9.26; N, 4.03.

4,17α-Dimethyl-4-aza-5α-androstan-17β-ol-3-one Acetate (V)—A solution of 1.00 g. of 4,17α-dimethyl-4-aza-5α-androstan-17β-ol-3-one (II) in 80 ml. of acetic anhydride was refluxed 1 hr. The acetic anhydride was evaporated *in vacuo*, and the residue, a yellow oil, was dissolved in ethyl ether. The solution was washed with a saturated sodium bicarbonate solution until effervescence ceased. After washing with water, the ether layer was dried over anhydrous sodium sulfate and taken to dryness *in vacuo*. Crystallization from acetone yielded 585 mg. (54%); m.p. 203–204°; $\lambda_{max.}^{CHCl_3}$ 5.8 and 6.1 μ.

Anal.—Calc. for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 73.18; H, 9.55; N, 3.86.

4,17α-Dimethyl-4-aza-5α-androstan-17β-ol Acetate (VI)—4,17α-Dimethyl-4-aza-5α-androstan-17β-ol (III) (100 mg., 0.3 mmole) was dissolved in 15 ml. of freshly distilled acetic anhydride, and the solution was refluxed for 30 min. The hot reaction mixture was poured into ice water with stirring. The crystals were filtered and recrystallized from methanol to yield 86 mg. (83%) of VI; m.p. 119.5–120°; $\lambda_{max.}^{CHCl_3}$ 5.78 μ.

[1] All melting points are uncorrected and were observed on a Thomas-Hoover or a Fisher-Johns melting-point apparatus. IR spectra were recorded by a Perkin-Elmer IR recording spectrophotometer. The UV spectra were recorded by a Beckman DB spectrophotometer. The elemental analyses were determined by Schwarzkopf Microanalytical Laboratory.



Scheme I

Anal.—Calc. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73; N, 4.03. Found: C, 75.68; H, 10.83; N, 3.98.

17α-Methyl-4-androsten-17β-ol-3-one *N*-Phenylcarbamate (VII)—To a chilled solution of 1.00 g. (3.3 mmoles) of methyltestosterone in 25 ml. of dry ethylbenzene was added 1.0 ml. (9 mmoles) of phenyl isocyanate. Vigorous refluxing under a nitrogen atmosphere was maintained for 30 hr. The solvent and excess phenyl isocyanate were completely removed *in vacuo*. The residue was crystallized from acetone to obtain 946 mg. (68%); m.p. 296–298°; λ_{max}^{KBr} 3.0, 5.78, 6.0, 13.1, and 14.3 μ.

Anal.—Calc. for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 76.89; H, 8.61; N, 3.72.

4,17α-Dimethyl-4-aza-5-androsten-17β-ol-3-one *N*-Phenylcarbamate (VIII)—To a chilled solution of 1.00 g. (3.2 mmoles) of 4,17α-dimethyl-4-aza-5-androsten-17β-ol-3-one (I) in dry ethylbenzene was added 1.0 ml. (9 mmoles) of phenyl isocyanate. Vigorous refluxing under a nitrogen atmosphere was maintained for 30 hr. The solvent and excess phenyl isocyanate were removed *in vacuo*, and the residue was crystallized from ethyl acetate–benzene to obtain 74 mg. (60%) of VIII as white crystals; m.p. 278–280°; λ_{max}^{KBr} 2.98, 5.75, 6.10, 13.10, and 14.25 μ.

Anal.—Calc. for $C_{27}H_{36}N_2O_3$: C, 74.28; H, 8.31; N, 6.42. Found: C, 74.02; H, 8.92; N, 6.31.

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