combined ether layers were washed with water, dried, and evaporated to give a colorless gum (1.53 g). The gum (1.40 g) was taken up in ethanol (100 mL), and concentrated HCl (2 mL) and 10% Pd on C (0.2 g) were added and hydrogenated overnight at atmospheric pressure. Filtration and evaporation gave a pale-yellow oil (1.1 g). The oil (1.0 g) was dissolved in concentrated HBr (20 mL), and the solution was refluxed for 5 h. It was then evaporated, azeotroped twice with benzene–methanol so as to remove most of the water, and crystallized from 1-butanol to give small pale-gray plates that were washed with 1-butanol and ether and dried thoroughly. The yield at this stage was 0.70 g, but the product contained 1-butanol on crystallization that was removed by recrystallization from ethanol–ether to give small off-white prisms (mp 254–256 °C) containing no butanol (GLC): MS m/e 193 ($C_{11}H_{15}NO_2$, 2%), 178 ($C_{10}H_{12}NO_2$, 100%). Anal. ($C_{11}H_{16}NO_2Br$) C, H, N.

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Apparent Bioisosteric Replacement of –S– by NCN: Synthesis of *N*-Cyano-2-aza-*A*-nor-5α-androstan-17β-ol Acetate, an Aza Steroid Androgen

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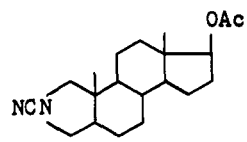
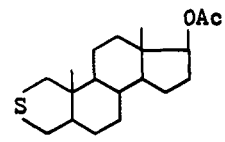
The synthesis of *N*-cyano-2-aza-*A*-nor-5α-androstan-17β-ol acetate is described. Cyclization of 1,4-dibromo-1,4-seco-2,3-bisnor-5α-androstan-17β-ol acetate with benzylamine in the presence of potassium iodide gives the *N*-benzyl-2-aza-*A*-nor steroid. Debenzylation with cyanogen bromide (Von Braun reaction) affords the *N*-cyano-2-aza-*A*-nor steroid, which has androgenic activity slightly weaker than that of the corresponding thia compound. The results indicate that NCN may be substituted for –S– as well as for =S. This compound is the first hormonally active steroid containing nitrogen as a heteroatom in the perhydrocyclopentanophenanthrene nucleus.

In previous papers from this laboratory the synthesis of various androgenic–anabolic heterocyclic steroids has been described.[1-4] Compounds containing sulfur and oxygen as heteroatoms and having one, two, or even three heteroatoms in ring A have been shown to be active. In all cases, we have concluded that it is the steric, rather than the electronic, properties of the ring atoms which are the determinants of pharmacological activity. For one class of heterocyclic steroids, however, the electronic properties may well be of overriding importance. There are the aza steroids in which the basic nitrogen atom could, either by virtue of its high electron density or by the formation of a cationic center, give rise to a biologically inactive compound. This may explain the lack of hormonal activity of the many aza steroids which have been synthesized.

A very recent study[5] on the histamine H_2-receptor antagonist, cimetidine, suggests that cyanoguanidine and thiourea may be classed as true bioisosteres owing to the close similarity of many of their physicochemical properties and the corresponding pharmacological parallelism of these groups with respect to histamine H_2-receptor antagonist activity. In these compounds, =NCN has been substituted for =S. This finding prompted us to synthesize *N*-cyano-2-aza-*A*-nor-5α-androstan-17β-ol acetate (1) as a possible bioisostere of thia steroid **2**. In this case, NCN would be substituted for –S–.



1



2

Dihydrotestosterone (**3**) (Searle) was acetylated with acetic anhydride in pyridine. Opening of ring A by CrO_3 oxidation gave 17β-acetoxy-2,3-seco-5α-androstane-2,3-dioic acid (**5**),[2,6] which via a modified Hunsdiecker reaction[7,8] afforded dibromide **6**. Dibromide **6** can be cyclized in the presence of a potent nucleophile such as S, Se, or Te with concomitant hydrolysis of the 17-protecting group.[1,2] In the present study, cyclization was unsuccessful with a weaker nucleophile such as benzylamine under the same conditions, but success was attained after addition of KI to the Me_2SO reaction mixture to convert the dibromo compound **6** into the corresponding diiodo compound. Under these conditions, the cyclization with benzylamine proceeded with retention of the 17-

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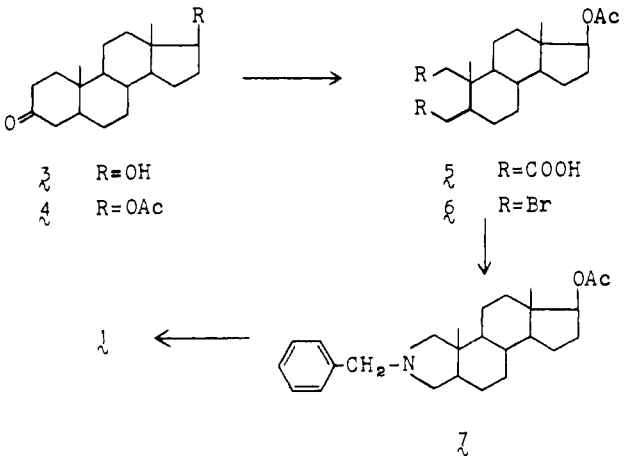
Table I. Androgenic-Myotrophic Assay

compd (total dose, mg)	wt, mg[a] ventral prostate	seminal vesicle	levator ani	body wt, g initial	final
castrate control	18.1 ± 0.91	11.4 ± 0.38	32.2 ± 1.82	56	98
testosterone (0.3)	35.3 ± 4.84	12.9 ± 0.51	37.8 ± 2.02	55	97
1 (3.0)	56.1 ± 6.96	33.3 ± 4.52	55.8 ± 1.60	55	95
1 (3.0) + testosterone (0.3)	61.6 ± 3.15	40.6 ± 1.74	58.7 ± 2.55	55	99
7	19.4 ± 1.55	10.7 ± 0.38	24.2 ± 0.43	55	89

[a] Means ± SE (average of five rats).



protecting group. Treatment of the *N*-benzylaza steroid **7** with cyanogen bromide in anhydrous benzene (von Braun reaction)[9] gave the *N*-cyano-2-aza-*A*-nor steroid **1** in good yield. The *N*-cyanoaza steroid **1** was more polar than the corresponding thia steroid on TLC.

The data from the pharmacological testing[10] are displayed in Table I. The *N*-cyano-2-aza-*A*-nor steroid **1** produced androgenic and myotrophic responses and was not antiandrogenic or antimyotrophic. Its androgenic activity is comparable to or only slightly weaker than that of the 2-thia-*A*-nor steroid (**2** acetate).[2] Compound **7** did not show any androgenic and/or myotrophic effect at the dose tested.

The results show that a biologically active *A*-nor steroid can be prepared by substituting cyanamide for sulfide. This is in harmony with our postulate of the importance of an A ring having atoms which flatten the ring in the vicinity of C-2 and C-3, or their replacement, for androgenic–myotrophic activity.[3] The data also suggest that NCN may be substituted bioisosterically for S (sulfide) in addition to the substitution for =S (thione) previously demonstrated.[5] The extension of these studies to a variety of other N-substituted 2-aza-*A*-nor steroids is in progress.

Experimental Section

***N*-Benzyl-2-aza-*A*-nor-5α-androstan-17β-ol Acetate (7).** A stirred solution of 1.8 g of **6**, 4.3 mL of benzylamine in 30 mL of Me_2SO, and 1.28 g of KI under N_2 gas was heated for 24 h in an oil bath kept at 100 °C. TLC showed the completion of the reaction. The reaction mixture was poured into 400 mL of ice–water, and the organic materials were extracted with Et_2O. The Et_2O extract was washed with water, dried over anhydrous Na_2SO_4, and evaporated to give an amber residue. Crystallization from acetone afforded 0.55 g of **7** in several crops: mp 114–119 °C; MS M^+ 396. Recrystallization from ether–hexane gave an analytical sample, mp 117–119 °C. Anal. ($C_{26}H_{37}NO_2$) C, H, N.

***N*-Cyano-2-aza-*A*-nor-5α-androstan-17β-ol Acetate (1).** A solution of 0.475 g of **7** in 5 mL of anhydrous benzene was treated with 0.13 g of cyanogen bromide at 27 °C, and the reaction mixture was heated under reflux for 1.5 h. TLC showed a single spot corresponding to **1** (R_f 0.41) using benzene–ethyl acetate (4:1) as the solvent system. In the same system, the thia steroid **2** had R_f 0.63. The solvent was evaporated under reduced pressure, and the residue was crystallized from hexane to give 0.25 g of **1**: mp 126–128 °C, MS M^+ 331. Recrystallization from ether–hexane afforded an analytical sample, mp 126–128 °C. Anal. ($C_{20}H_{30}N_2O_2$) C, H, N.

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