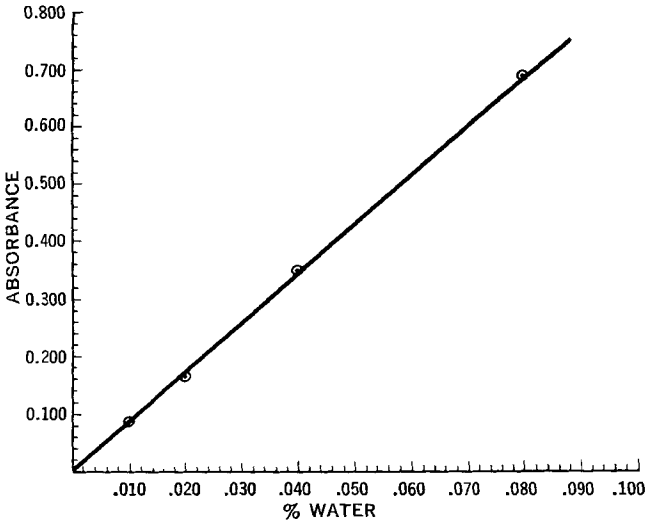


**Figure 2**—*Calibration or working plot obtained from the values in Fig. 1 plotted against concentration.*

amounts of water, and free from interferences. In addition, it makes it possible to determine water down to the level of 0.05% based on an initial sample weight of 2.5 g.

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# Aminosteroids

**ARVIN P. SHROFF**

**Abstract** □ Synthesis of 17β-acetamido-6α,16α-dimethylandrost-4-en-3-one and 3-aza-17β-acetamido-6α,16α-dimethylandrost-4a-en-4-one *via* Beckmann and Schmidt rearrangement has been described. Both of these compounds were judged inactive when subjected to Herschberger androgen-anabolic assay.

**Keyphrases** □ 17β-Acetamido-6α, 16α-dimethylandrost-4-en-3-one—synthesis □ 3-Aza-17β-acetamido-6α, 16α-dimethylandrost-4a-en-4-one—synthesis □ UV spectrophotometry—identity □ IR spectrophotometry—identity

Torizuka *et al.* (1) while investigating the dynamics of protein metabolism in man, found that anabolic steroids such as 19-nor-testosterone phenylpropionate and 4-chlorotestosterone acetate, did not inhibit degradation of protein but exclusively stimulated its synthesis. The primary site of action is possibly at the nuclear level for the production of RNA's essential for protein biosynthesis (2). There are a large number of theoretical possibilities by which an androgen molecule can stimulate this RNA production. One of them suggested by Hübener (3) would be to inhibit a repressor aimed at an operator gene and controlled by a regulator gene. The interaction between androgen molecule and protein has been reported by Westphal (4) and that this interaction is on the β-face of the steroid molecule was suggested by Wolff *et al.* (5).

This work was initiated to investigate this hypothesis and to see if creation of high electron densities in Ring A and D would impart or enhance biological response. 6α,16α-Dimethylprogesterone was chosen for these molecular modifications. Treatment of I with pyrrolidine gave the enamine II which could be converted into 20-oximino Compound III with hydroxylamine hydrochloride. Beckman rearrangement of III using thionyl chloride, followed by acid hydrolysis gave the desired 17β-acetamido-6α,16α-dimethylandrost-4-en-3-one (IV). Compound I when subjected to Schmidt rearrangement gave 3-aza-17β-acetamido-6α,16α-dimethylandrost-4a-en-4-one (V). The spectral data confirmed all the structural assignments. Compounds IV and V were subjected to Herschberger androgen-anabolic assay (6) and judged inactive (see Scheme I).

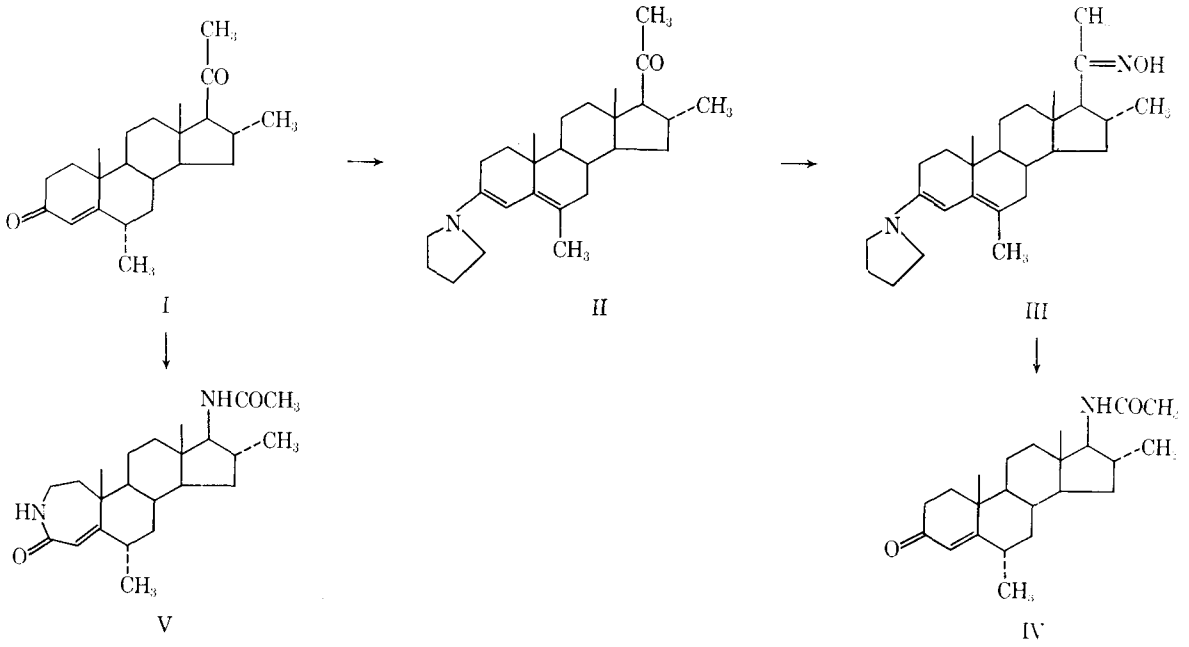
## EXPERIMENTAL

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The UV and IR data were obtained on Cary Model 11 and Beckman IR-5 spectrophotometers, respectively. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

**3-[1-Pyrrolidinyl]-6-16α-dimethylpregn-3,5-dien-20-one (II)**—Two grams of I was dissolved in 10 ml. of MeOH with heat and treated with 10 drops of pyrrolidine. Heating was continued for an additional 5 min. when copious precipitates of enamine separated. The precipitates were collected by filtration, washed several times with MeOH and dried to give 1.8 g. (77%) of II, m.p. 137–139°; $\lambda_{max.}^{EtOH}$ 278 mμ; $\lambda_{max.}^{KBr}$ 5.88, 6.1, and 6.23μ.

*Anal.*—Calcd. for $C_{27}H_{41}NO$: N, 3.54. Found: N, 3.23.

**3-[1-Pyrrolidinyl]-6,16α-dimethylpregn-3,5-dien-20-one oxime (III)**—A mixture containing 1.7 g of II, 500 mg. of $NH_2OH \cdot HCl$ in 5 ml. of pyridine was heated on a steam bath for 1.5 hr. and poured



*Scheme I*

over a large amount of ice water. The solid thus separated was collected by filtration and recrystallized from MeOH-$H_2O$ to yield 1.5 g. (88%) of III, m.p. 171–173°. $\lambda_{max.}^{EtOH}$ 279mμ; $\lambda_{max.}^{KBr}$ 3.01 and 6.11μ.

*Anal.*—Calcd. for $C_{27}H_{42}N_2O$: N, 6.82. Found: N, 6.87.

**17β-Acetamido-6α,16α-dimethylandrost-4-en-3-one (IV)**—A dioxane solution of 3.0 g. of III was treated with 1.0 ml. of $SOCl_2$ and the mixture stirred for 0.5 hr. It was poured over a large amount of ice water and neutralized with NaOH solution. The neutral solution was extracted with $CH_2Cl_2$ and the organic layer was thoroughly washed with $H_2O$, dried ($Na_2SO_4$), and evaporated to give an oil. $\lambda_{max.}^{EtOH}$ 278 mμ; $\lambda_{max.}^{NaCl}$ 3.0 and 6.0μ.

The oil was hydrolyzed with 25 ml. of 5% methanolic $H_2SO_4$ by refluxing the solution for 2 hr. Evaporation of excess alcohol and pouring the concentrate into a large amount of ice water gave solid residue. It was collected by filtration and subjected to column chromatography on neutral alumina. Elution with 50% $CH_2Cl_2$–$Et_2O$ gave IV m.p. 205–207°. $\lambda_{max.}^{EtOH}$ 240 mμ; $\lambda_{max.}^{KBr}$ 2.99, 5.99 and 6.05μ.

*Anal.*—Calcd. for $C_{23}H_{35}NO_2$: C, 77.26; H, 9.87; N, 3.92. Found: C, 77.55; H, 9.78; N, 3.36.

**3-Aza-17β-acetamido-6α,16α-dimethylandrost-4a-en-4-one (V)**—Compound I (5.0 g.) was added by 150 g. of polyphosphoric acid (PPA) and was maintained at 55°. To this 5.0 g. of $NaN_3$ was added in small portions over a period of 1–5 hr. with intermittent stirring. The mixture was allowed to remain at about 55° for 7 hr. and the PPA then decomposed with $H_2O$. The solution was neutralized with 25% NaOH solution and extracted with $CH_2Cl_2$. The organic phase was washed several times with $H_2O$, dried ($Na_2SO_4$), and evaporated. The residue was recrystallized from $CH_2Cl_2$–$Et_2O$ to give 2.5 g. (50%) of V, m.p. 167–170°. $\lambda_{max.}^{EtOH}$ 218 mμ; $\lambda_{max.}^{KBr}$ 3.0; 6.02μ.

*Anal.*—Calcd. for $C_{23}H_{36}N_2O_2$: C, 74.15; H, 9.74; N, 7.52. Found: C, 74.18; H, 10.01; N, 7.31.

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