and subsequently bond, by means of the alkylating groups, to, for example, the active site of enzymes for which guanine is a substrate.

Experimental Section

Nmr.—The nmr of III was determined in DMSO-d_6 with Me_4Si as the internal standard. H were assigned as shown in Table I. Upon addition of D_2O the peaks at δ 7.50 and 8.0 disappeared.

TABLE I

ASSIGNMENT OF HYDROGENS

Type H	δ value	Ratio	Splitting
a	3.95	2	Distorted triplet
b	4.35	6	Distorted triplet
c	4.60		Distorted triplet
d	7.60	1	Singlet
e	7.50 or 8.0	?	Broad humps
f	7.50 or 8.0	?	Broad humps

Mass Spectrum.—The mass spectral fragmentation pattern showed the molecular ion peak to occur at m/e 242, which corresponds to the positive ion III.

Crystal Data and Structure Determination.—The transformation product was recrystallized (MeOH) to give thick tabular yellow crystals (001) with a = 12.80, b = 7.41, c = 12.42 Å; β = 90°44′; V = 1178 Å^3; D_m (flotation) 1.58; Z = 4; D_x 1.573; absorption coefficient for CuKα radiation, 49.5 cm^{-1}. The crystal size was 0.2 × 0.2 × 0.2 mm. Intensity data were measured with a Picker four-circle automatic diffractometer in θ–2θ mode to a maximum 2θ of 130°. Systematic extinctions for $0k0$ (k odd) and $h0l$ (l odd) indicated, unambiguously, the monoclinic space group $P2_1/c$. The structure was solved using Patterson and heavy-atom methods and refined by block diagonal least squares to give an agreement factor R of 0.20. Further anisotropic full-matrix least-squares refinement has reduced the R factor to 0.10 and permitted the determination of H-atom positions by the difference Fourier method.

3-Aza-A-homoandrostenes

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One of the views on the mechanism of steroid hormone action is that steroids exert their effect at the level of DNA control of RNA synthesis.[1] The messenger RNA molecules thus are the templates for *de novo* enzyme synthesis and it is these enzymes which regulate the process resulting in the observed physiological effects.[2] The interaction between steroid and DNA[3-5] and steroid and protein[6] is well established. In fact, Ts'o and Lu[7] have demonstrated that the coil form of DNA has a higher affinity for steroids than the helical form. These types of findings prompted Ringold[8] to postulate an α-face adsorption for androgen molecules. In contrast, Wolff and coworkers[9] have proposed two discrete areas of adsorption: the β face for rings A, B, and C and the α face for ring D. Both of these authors[8,10] have indicated a β-face adsorption for progestational agents.

We were interested in exploring these findings using the androgen, ethisterone, as our starting compound for molecular modification. The progestational activity of this compound was of interest to us because although only one-third as active as progesterone, it exhibited oral activity. Alteration of the A ring of ethisterone to a seven-membered ring containing nitrogen would increase the π-bonding characteristics of the molecule and could conceivably enhance the nonbonded adsorption to the receptors. Hence, ethisterone was converted to its acetate by the procedure of Yamada[11] and transformed to compounds **1**–**5** (Scheme I) by methods described in the Experimental Section.

The progestational activity of these compounds was determined by the Clauberg test[12] and the endometrial response was scored according to the index of McPhail.[13] Ethisterone showed a McPhail index of 0.8 at a 5-mg dose, whereas both **2** and **3** exhibited 0 response at the same dose levels. These results, though limited in nature, perhaps do point out that in the androgen molecule the expansion of the A ring alters the site of π complex with the receptor (β face) and thus decreases the activity. Compounds **4** and **5** were also subjected to androgen–anabolic assay[14] and were found to have only 5% the activity of methyltestosterone. The decrease in activity can probably be attributed to steric effects in ring A (β face) and at C-17 (α face). No data are available at present on the mode of action of these aza steroids, but it is possible that these compounds may act at the protein level by inducing a modification in the enzyme which regulates the physiological effect.

Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The uv and ir data were obtained on a Cary Model 11 and Beckman IR-5 spectrophotometers, respectively. The nmr spectra were determined on a Varian A-60 spectrometer in $CDCl_3$ using TMS as an internal standard (0 ppm). All parts per million values are the center of the signals. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

3-Oximino-17α-ethynyltestosterone Acetate (1).—A solution containing 2.0 g of 17α-ethynyltestosterone acetate, 1.0 g of $HONH_3^+Cl^-$, and 10 ml of pyridine was heated on a steam bath for 0.5 hr. The mixture was poured into 300 ml of ice–water and the solid thus precipitated was collected by filtration. Recrystallization (MeOH–H_2O) gave 1.95 g (94%) of **1**: mp 183–185°; $[\alpha]D$ +75.2°; λ_{max}^{KBr} 2.92, 3.04, 5.69, and 6.1 μ; λ_{max}^{EtOH} 238 mμ; pmr ($CDCl_3$), 0.91 (C-18), 1.1 (C-19), 2.03 (C-17, OAc), 2.57 (C-17, C≡CH), 5.81 (C-4 *syn*), and 6.5 ppm (C-4 *anti*). *Anal.* ($C_{23}H_{31}NO_3$) C, H, N.

Preparative tlc of the oxime isomers was carried out on silica gel G (750-μ thickness) and estimated by titrating (with Radiometer) each eluent (*syn* and *anti*) with 0.5 N $HClO_4$. The

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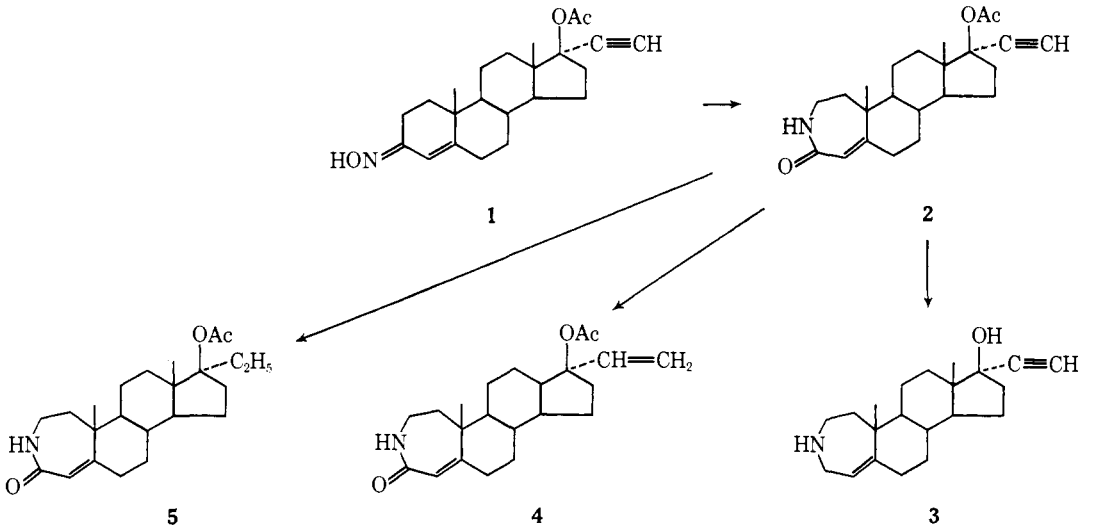
SCHEME I



syn isomer (lower streak) was found to be 30% and the *anti* isomer was 70%.

3-Aza-17α-ethynyl-17β-acetoxy-A-homoandrost-4a-en-4-one (2).—To a solution containing 17.6 g of 1 in 500 ml of purified dioxane there was added 10 ml of $SOCl_2$. The mixture was stirred at room temperature for 1.5 hr and poured into a large amount of water. The excess acid was neutralized with $NaHCO_3$ and the solution was extracted (CH_2Cl_2). The organic layer was washed (H_2O), dried (Na_2SO_4), and filtered. The filtrate was stirred for 3 hr with 150 g of IR-45 Amberlite (Rohm and Hass) and filtered. The filtrate was evaporated to give a semisolid which could be recrystallized from C_6H_6–C_6H_{14} (1:3) to give 4.4 g (83% based on *syn* isomer) of **2**: mp 245–247°; $[\alpha]D$ −41.1°; $\lambda_{max}^{CHCl_3}$ 2.9, 3.0, 5.73, and 6.05 μ; λ_{max}^{EtOH} 220 mμ; pmr ($CDCl_3$), 0.9 (C-18), 1.17 (C-19), 2.03 (C-17, OAc), 2.58 (C-17, C≡CH), and 5.72 ppm (C-4a). *Anal.* ($C_{23}H_{31}NO_3$) C, H, N.

3-Aza-17α-ethynyl-A-homoandrost-4a-en-17β-ol (3).—To a solution of 3.5 g of **2** in 150 ml of THF there was added over a period of 1 hr 7.0 g of $LiAlH_4$. The mixture was refluxed for 26 hr with continuous stirring. The excess $LiAlH_4$ was decomposed with Et_2O saturated with H_2O followed by H_2O. The mixture was filtered and the inorganic hydroxides were washed with EtOAc. The filtrates were combined, washed (H_2O), dried (Na_2SO_4), and evaporated. The solid residue was warmed with alcoholic KOH and poured into a large amount of H_2O. The solid thus separated was collected by filtration and recrystallized from EtOAc to give 1.4 g (40%) of **3**: mp 206–208°; $[\alpha]D$ −41°; $\lambda_{max}^{CHCl_3}$ 2.78 and 3.01 μ, no uv absorption between 200 and 360 mμ; pmr ($CDCl_3$), 0.87 (C-18), 1.1 (C-19), 2.55 (C-17, C≡CH), and 5.41 ppm (C-4a). *Anal.* ($C_{21}H_{31}NO$) C, H, N.

3-Aza-17α-vinyl-17β-acetoxy-A-homoandrost-4a-en-4-one (4).—One gram of **2** was dissolved in 10 ml of pyridine and treated with 200 mg of 5% Pd–C. The mixture was hydrogenated at room temperature and atmospheric pressure until 1 mole of H_2 was consumed. It was filtered and the filtrate was poured over a large amount of ice and H_2O. The solid thus separated was collected by filtration and recrystallized from EtOAc to give 1.0 g (99%) of **4**: mp 238–240°; $[\alpha]D$ +8.7; $\lambda_{max}^{CHCl_3}$ 2.90, 5.75, and 6.05 μ; λ_{max}^{EtOH} 220 mμ; pmr ($CDCl_3$), 0.98 (C-18), 1.16 (C-19), 2.0 (C-17, OAc), 5.14 (C-17, vinyl multiplets), and 5.72 ppm (C-4a). *Anal.* ($C_{23}H_{33}NO_3$) C, H, N.

3-Aza-17α-ethyl-17β-acetoxy-A-homoandrost-4a-en-4-one (5).—Two grams of **2** was dissolved in 20 ml of AcOH and treated with 1 g of 5% Pd–C. The mixture was hydrogenated at room temperature and atmospheric pressure until 2 moles of H_2 was consumed. It was filtered and the filtrate was poured over ice and H_2O. The solid thus separated was collected by filtration and recrystallized from EtOAc to give 1.7 g (87%) of **5**: mp 248–250°; λ_{max}^{KBr} 3.1, 5.75, and 6.0 μ; λ_{max}^{EtOH} 220 mμ; pmr ($CDCl_3$), 0.88 (C-18), 1.17 (C-19), 2.0 (C-17, OAc), and 5.72 ppm (C-4a). *Anal.* ($C_{23}H_{35}NO_3$) C, H, N.

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Compounds Related to Insect Juvenile Hormone

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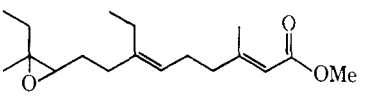
The structure of the insect juvenile hormone (JH) obtained from the cecropia moth, *Hyalophora cecropia* L., has recently been reported as I,[1] and I has been synthesized and found to be highly active.[2,3] Previously, methyl farnesate 10,11-epoxide (II)[4] and methyl 7,11-dichloro-3,7,11-trimethyl-2-dodecenoate (III)[5,6] were also found to be highly active.



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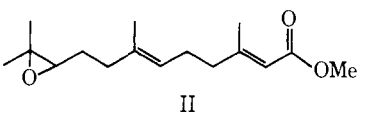

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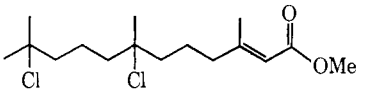

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