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THE SYNTHESIS OF STEROIDAL [16α,17α-d]-2′-PYRAZOLINES AND [16,17-d]-PYRAZOLES

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Abstract—The addition of diphenylnitrilimines to a series of steroidal 16,17-dipolarophiles occurs with the same regio specificity in all cases regardless of the nature of the 17-substituent, to yield [16α, 17α-d]-2′pyrazolines. The adducts from the 17-acetoxy-16,17-androstene, **3c**, cannot be isolated but yield the [16,17-d]-pyrazoles by loss of acetic acid.

Previous syntheses of steroidal pyrazoles and pyrazolines have employed the condensation of hydrazines with α-hydroxymethylene ketones and their derivatives[1,2] the cyclization of hydrazones of α,β-unsaturated ketones[3] the treatment of α,β-epoxy-ketones with hydrazine[4] and the 1,3-dipolar addition of aliphatic diazo-compounds to α,β-unsaturated ketones.[5] Some of the resulting compounds have demonstrated biological activity.[6]

In the present study the title compounds have been synthesized by the 1,3-dipolar addition of diphenylnitrilimines[7] to 17-substituted 16,17-androstenes with the twofold objective of preparing compounds with biological activity and of studying the regiochemistry of the process. The 16,17-unsaturated steroidal system was considered an attractive platform for studying the interplay of steric and electronic effects in this type of addition reaction. When this study was started there was no satisfactory explanation of the observed regioselectivity in 1,3-dipolar cyclo-additions. Both electronic and steric effects had been invoked to rationalize the isomer ratios.[8] Since then Houk[9] and Bastide[10] have successfully used perturbation theory to explain regio selectivity for a wide range of 1,3-dipolar additions. Houk[9] has stated that "orientation phenomena can all be explained more or less satisfactorily by electronic effects alone". On the other hand, Huisgen[11] in a recent review has emphasized how orientations in the addition of diphenylnitrilimine to α,β-unsaturated esters can easily be reversed. For example the addition of diphenylnitrilimine to methyl acrylate produces exclusively the 5-carbomethoxy-substituted pyrazoline, **1a**, whereas methyl crotonate yields a mixture of the 5-substituted isomer, **1b**, and the 4-substituted isomer, **2a**, in the ratio 64:36. In the case of methyl β,β-dimethylacrylate the 4-substituted isomer, **2b**, is the major product, outweighing the 5-isomer, **1c**, by a ratio of 9:1.[7]

For 17-substituted-16,17-androstenes (**3a–f**) electronic effects[9,10] dictate that addition of diphenylnitrilimines should lead to [16α,17α-d]-2′-pyrazolines **4** for both electron-withdrawing (**3a, b, e**) and electron-donating substituents (**3c, d**). Previously invoked steric effects have concerned only the degree of substitution of the dipolarophilic double bond.[7] From this standpoint it is not easy to make meaningful comparisons of the 17-substituted-16,17-androstenes with simpler systems. We know of no cases of additions of nitrilimines to methyl 2,3-dimethyl-acrylate, the obvious compound for comparison, or to the corresponding methyl ketone. It might be suggested that the addition of alkyl groups of approximately the same bulk to both carbon atoms of methyl acrylate would have a neutralizing effect and that the regiochemical outcome in an addition reaction would be the same as for methyl acrylate itself. In the case of 17-substituted-16,17-androstenes, however, longer-range steric effects would be more important. Huisgen[12] has pointed out that the carbon terminus of diphenylnitrilimines has the larger steric requirement and Dreiding models indicate that in the parallel-plane approach of dipole and dipolarophile the 12α-H will offer considerable steric interference, leading, as for the electronic effect, to the formation of the [16α,17α-d] regioisomers.

Addition of triethylamine to a mixture of 3β-acetoxypregna-5,16-dien-20-one **3a** and benzoyl chloride phenylhydrazone led to a 65% yield of 3β-acetoxypregna-5-en-20-ono-[16α,17α-d]-1′,3′-diphenyl-2′-pyrazoline **4a** as predicted. In the IR spectrum the 20-keto group absorbed at 1711 cm^{-1}, typical of a saturated ketone, and there were prominent absorptions at 1598, 750 and 690 cm^{-1} characteristic of monosubstituted benzene rings. The UV spectrum showed maxima at 372, 322, 310 and 245 nm typical of 1,3-diphenyl-2-pyrazolines[13] and the solutions showed noticeable fluorescence.[14] The mass spectrum showed a molecular ion at 550 and a prominent fragment at 507 (M^+–CH_3CO).

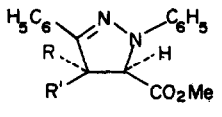
It had been planned to establish the regiochemistry of the adduct by comparison of the chemical shifts of the 16βH and hydrogens 3a and 7a of adduct **5** formed from diphenyl nitrilimine and norbornene.[8a] Unfortunately the chemical shift (4.28) of the 16β-H fell between the values for the 3a and 7a hydrogens, undoubtedly as a result of the anisotropy of the 20-carbonyl group.[15]

A study of the ^1H NMR data for a series of C-phenyl-(**4b–f**) and *N*-phenyl-(**4g, h**) substituted adducts showed that for all compounds with the exception of the *N*-*o*-chloro compound **4g** the chemical shift values for the 18-CH_3 groups were identical and that for all compounds other than the *C*-*o*-chloro (**4b**) and *C*-*o*-bromo (**4c**) adducts the 16βH signal occurred at 4.20 ppm. These data indicated that all of the diphenylpyrazolino steroids possessed the same regiochemistry and stereochemistry. This was strongly confirmed by circular dichroism data which showed for all compounds very strong positive Cotton effects between 354 and 370 nm and very strong negative effects between 310 and 322 nm.[16] The pronounced downfield shift (0.5 ppm) of the 16β-H

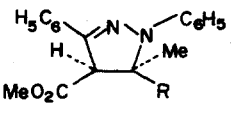
(4.70δ) in both the *C*-*o*-chloro (**4b**) and *C*-*o*-bromo (**4c**) adducts proved the regiochemistry of the addition since in the predominantly planar[14] 1′,3′-diphenyl-2′-pyrazoline structure the *ortho*-substituent of the C-phenyl ring will be in close spatial proximity to the 16β-H in the preferred "inside" conformation, **6a**. The "outside" conformation, **6b** would presumably be destabilized by electrostatic repulsion from the 2′-nitrogen atom of the pyrazoline ring. Through space deshielding effects by halogens have been described by Gribble[17] and Mathieson.[18] The above conclusion was reinforced by the fact that the 18- and 21-CH_3 groups were deshielded, as expected, in the *N*-*o*-chloro adduct (**4g**).

Although the stereochemistry of the addition can be safely assumed by comparison with other cycloadditions at 16,17[19] it was confirmed by 90 MHz examination of the 16β-H in **4a**. The sum of the coupling constants ($J_{AX}+J_{BX}$) for the partially resolved signal was 9.3 Hz in accord with the dihedral angles (10°, 110°) subtended by the 15 hydrogens (calculated sum 8.0H_2). For a 16α-H the calculated sum for angles of 22° and 140° is 12.3 Hz. The stereochemistry was confirmed indirectly by the observation that adduct **4a** was inert to hydrogenation conditions (10% Pd/C, atmospheric pressure) which normally produce rapid saturation of the 5,6 double bond. This lack of reactivity is attributed to the inability of the steroid to seat itself on the catalyst surface because of the considerable bulk of the α-oriented diphenylpyrazoline system. Hydrogenation did proceed under more forcing conditions (Pt, H^+) to produce **7** in which the phenyl rings had been reduced to cyclohexanes and the AB ring junction was *cis* as shown by the NMR signal of the 3α-H (5.18; W/2, 5 Hz). This almost certainly occurred by prior isomerization of the double bond to 4,5 followed by the usual β-hydrogenation[20] of this system.

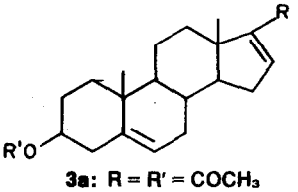
Diphenylnitrilimine also added readily to the phenylketone **3f**, which was prepared by way of the reaction of 3β - acetoxy - 17 - cyanoandrosta - 5,16 - diene, **3b**, with phenylmagnesium bromide. The bright yellow adduct, **8a**, showed similar CD behavior to that of the methylketones, **4a–h**, except that the strong positive and negative Cotton effects were shifted to 400 and 338 nm respectively. The corresponding *C*-*o*-chloro adduct, **8b**,



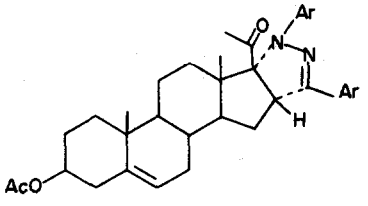
1a: R = R′ = H
b: R = CH_3, R′ = H
c: R = R′ = CH_3



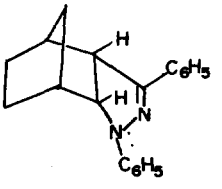
2a: R = H
b: R = CH_3



3a: R = R′ = $COCH_3$
b: R = CN, R′ = $COCH_3$
c: R = OAc, R′ = $COCH_3$
d: R = OCH_3, R′ = $COCH_3$
e: R = COC_6H_5, R′ = H
f: R = COC_6H_5, R′ = $COCH_3$



4a: Ar = Ar′ = C_6H_5
b: Ar = C_6H_5, Ar′ = *o*-Cl-C_6H_4
c: Ar = C_6H_5, Ar′ = *o*-Br-C_6H_4
d: Ar = C_6H_5, Ar′ = *m*-Cl-C_6H_4
e: Ar = C_6H_5, Ar′ = *p*-Cl-C_6H_4
f: Ar = C_6H_5, Ar′ = *p*-CH_3O-C_6H_4
g: Ar = *o*-Cl-C_6H_4, Ar′ = C_6H_5
h: Ar = *p*-Cl-C_6H_4, Ar′ = C_6H_5



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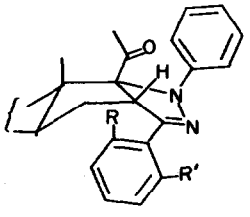
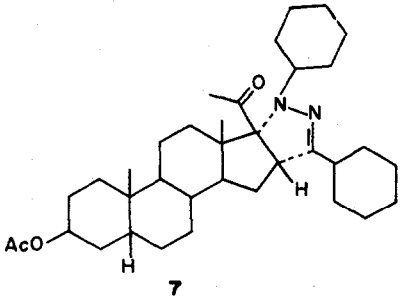


6a: R = Cl, R′ = H
b: R = H, R′ = Cl



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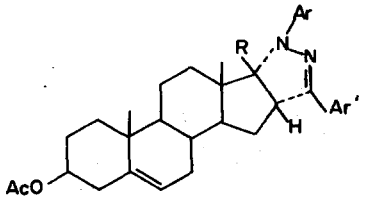


8a: R = COC_6H_5, Ar = Ar′ = C_6H_5
b: R = COC_6H_5, Ar = C_6H_5, Ar′ = *o*-Cl-C_6H_4
c: R = OCH_3, Ar = Ar′ = C_6H_5
d: R = OAc, Ar = Ar′ = C_6H_5

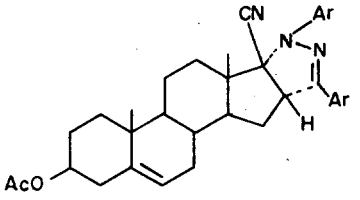
showed the expected downfield shift (0.41 ppm) of the 16β-H thus confirming the regiochemistry of this cycloaddition.

Addition of diphenylnitrilimine to 3β-acetoxy-17-cyanoandrosta-5,16-diene, **3b**, took place in the same regiochemical sense as for the 20-ketopregnene, **3a**, to yield 3β-acetoxy-17β-cyanoandrost-5-eno-[16α,17α-d]-1',3'-diphenyl-2'-pyrazoline, **9a**. The *C*-*o*-methyl adduct, **9b**, was prepared in like fashion. To probe the "ortho-halogen effect" referred to above, the *C*-*o*-fluoro, **9c**, *C*-*o*-chloro, **9d**, and *C*-*o*-bromo, **9e**, adducts were compared. As anticipated the signal of the 16-H moved downfield from 4.47 for the unsubstituted compound, **9a**, to 4.65 for the *o*-fluoro, 4.92 for the *o*-chloro and 4.95 ppm for the *o*-bromo adduct. In all 17-cyano products the 18-CH_3 group appeared at 1.28–1.30δ. Pyrolysis of 3β-acetoxy-17β-cyanoandrost-5-eno-[16α,17α-d]-1',3'-diphenyl-2'-pyrazoline, **9a**, at 290°, led to elimination of HCN and the formation of 3β-acetoxyandrost-5-eno-[16,17-d]-diphenylpyrazole **10a**, which showed an intense parent ion at *m/e* 506 and the absence of an NMR signal for a 16-hydrogen atom.

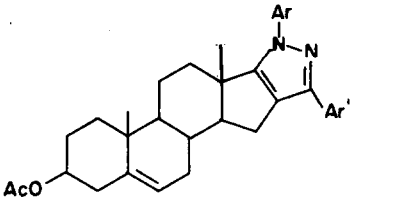
To confirm the regiochemistry of pyrazole **10a** its regioisomer was prepared as follows. 3β-Acetoxy-17-benzoylandrost-5,16-diene **3f** was converted to its phenylhydrazone, **11**, followed by cyclization with ethanolic hydrochloric acid to the diphenyl-pyrazoline, **12b**, which was dehydrogenated with dichlorodicyanobenzoquinone to 3β-acetoxyandrost-5-eno-[17,16-d]-1',3'-diphenylpyrazole **13**, which differed in m.p. IR, NMR, UV and optical rotatory properties from its regioisomer, **10a**.

To study the regiochemistry of addition to steroidal 16,17-olefins carrying an electron donating substituent at C-17 3β-acetoxy-17-methoxyandrosta-5,16-diene **3d** was prepared by pyrolysis of the dimethylketal, **14**.[21] Addition of diphenylnitrilimine to 3β-acetoxy-17-methoxy-androsta-5,16-diene, **3d**, gave 3β-acetoxy-17β-methoxy-androst-5-eno[16α,17α-d]-1',3'-diphenyl-2'-pyrazoline **8c**, which showed a parent ion at *m/e* 538 and a base peak at *m/e* 446, corresponding to loss of acetic acid from the A ring and methanol from the D ring. The ease of aromatization of this compound was shown by the fact that it displayed a double melting point, the higher value corresponding to the melting point of pyrazole **10a**. The regiochemistry was proved conclusively by smooth pyrolysis at 260° to pyrazole **10a**. Pyrolysis at 300° led to additional loss of acetic acid to give androsta-3,5-dieno-[16,17-d]-1',3'-diphenylpyrazole **15**.

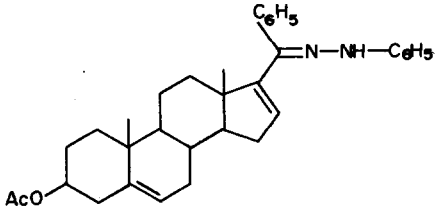
The enol acetate, **3c**, underwent addition of diphenyl-



9a: Ar = Ar' = C_6H_5
b: Ar = C_6H_5, Ar' = *o*-CH_3-C_6H_4
c: Ar = C_6H_5, Ar' = *o*-F-C_6H_4
d: Ar = C_6H_5, Ar' = *o*-Cl-C_6H_4
e: Ar = C_6H_5, Ar' = *o*-Br-C_6H_4



10a: Ar = Ar' = C_6H_5
b: Ar = C_6H_5, Ar' = *p*-ClC_6H_4
c: Ar = *p*-Cl-C_6H_4, Ar' = C_6H_5



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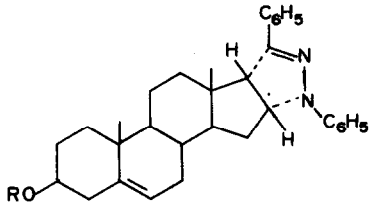
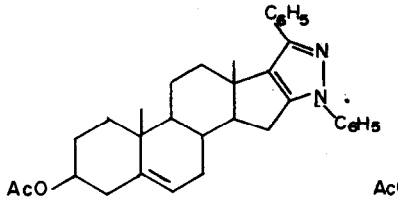


12a, R=H
b, R=$COCH_3$



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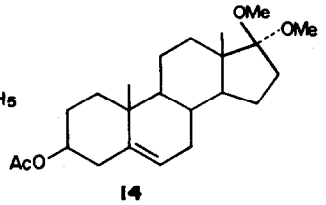

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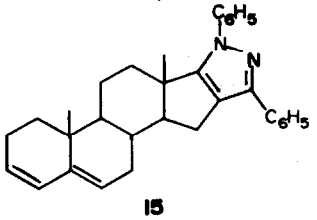

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nitrilimine rather slowly to give a low yield (30%) of pyrazole, **10a**. Obviously in this case the initially formed pyrazoline underwent spontaneous loss of acetic acid. This was not surprising in view of the good leaving group characteristics of acetate and the driving force of aromatization. In similar fashion the *C-p*-chloro-**10b** and *N-p*-chloro-**10c** pyrazoles were prepared in yields of 5 and 17% respectively.

Thus it has been demonstrated that the addition of diphenylnitrilimines to steroidal 17-substituted-16-olefins occurs in the same regiospecific sense regardless of the electronic nature of the 17-substituent. This is in accord with both electronic and stereochemical predictions. Work will be reported shortly on the corresponding addition reactions to steroidal systems in which electronic and stereochemical effects are in opposition.

EXPERIMENTAL

M.ps (Thomas–Hoover unit) are uncorrected. IR spectra were obtained on a Perkin–Elmer 457 instrument. UV spectra were run on a Perkin–Elmer 202 spectrophotometer. Most NMR spectra ($CDCl_3$) were recorded on a Varian A-60 spectrometer; the 90 MHz data were obtained on a Bruker 90 instrument[22] at the University of Bonn. Chemical shifts (δ) are given in ppm downfield from internal TMS. Mass spectra were taken on a Dupont 491 instrument equipped with a direct inlet. CD spectra were obtained on a Roussel-Jouan Dichrographe, Mark II[22] and on a Carey 60 spectropolarimeter. Silicagel HF_{254} (E. Merck) was used for TLC analysis. Microanalyses were performed by Alfred Bernhardt Laboratories, Elbach über Engelskirchen, W. Germany, and by Galbraith Laboratories, Knoxville, Tennessee.

2-Bromobenzoyl chloride phenylhydrazone. To a suspension of 2-bromobenzoyl phenylhydrazide (14.55g; 0.05 mole) in anhydrous ether (300 ml) was added PCl_5 (12.22g; 0.0585 mole). The reaction mixture was stirred for 72 h at room temp. during which time solution occurred. Phenol (15.5g, 0.176 mole) was added to the brown solution with stirring followed after 30 min by methanol (20 ml). Evaporation at 60° gave an oil which was chromatographed on silicagel in 1/1 hexane/toluene. The first fractions contained the product as an oil which solidified (10.58g, 68%), pure by TLC. An analytical sample was recrystallized twice from methanol and then twice from heptane as prisms, m.p. 58–60°; IR (neat): 3340(m), 3060, 3038(w), 1605(s), 1595(sh), 1505(s), 1260(s), 1138(s), 938(s), 745(s), 688(s) cm^{-1}. (Found: C, 50.38; H, 3.40; Br 25.72, Cl, 11.32; N, 8.99. Calc. for $C_{13}H_{10}BrClN_2$: C, 50.43; H, 3.26: Br, 25.81; Cl, 11.45; N, 9.05%.)

2-Fluorobenzoylphenylhydrazide. 2-Fluorobenzoyl chloride (25g, 0.158 mole) was added dropwise with stirring to an ice-cold solution of phenylhydrazine (17g, 0.157 mole) in dry pyridine (150 ml). The mixture was allowed to attain room temperature and maintained there for 20 h. The reaction mixture was poured into ice-water and the product recrystallized from methanol/water as cream needles (21.5g, 59%), m.p. 140–142°. The analytical sample was recrystallized from methanol as needles, m.p. 140.5–142°. IR (Nujol) 3360(m), 3280(m), 1630(s), 1610, 1600 (s, sh), 1545(m), 1500, 1460, 1400(s), 1300(m), 1270, 1218(m), 1100(w.m), 758(s), 741(s), 691(s) cm^{-1}. (Found: C, 67.98; H, 4.90; N, 12.09; F, 8.37. Calc. for $C_{13}H_{11}FN_2O$: C, 67.82; H, 4.82; N, 12.17; F, 8.25%.)

2-Fluorobenzoyl chloride phenylhydrazone. The reaction was carried out exactly as for the 2-bromo analog using 11.5g (0.05 mole) of 2-fluorobenzoylphenylhydrazide, 12.22g (0.0585 mole) phosphorous pentachloride and ether (400 ml). The product was chromatographed on silicagel to give 2-fluorobenzoyl chloride phenylhydrazone (3.49g, 29%). Recrystallization from hexane gave the analytical specimen as cream prisms, m.p. 82–83.5°. IR ($CHCl_3$): 3340(m), 3062, 3018(w), 1600(s), 1500(s), 1318(s), 1281(s), 1263(s), 1240(s), 1225(s), 1145(s), 948(s), 690(s) cm^{-1}. (Found: C, 62.90; H, 3.99; N, 11.35; Cl, 14.21; F, 7.70. Calc. for $C_{13}H_{10}N_2ClF$: C, 62.79; H, 4.06; N, 11.26: Cl, 14.25; F, 7.64%.)

3β-Hydroxy-17-benzoylandrost-5,16-diene **3e**. A solution of 3β-acetoxy-17-cyanoandrost-5,16-diene[23] (**3b**, 5g., 14.75 mmole) in ether (150 ml) was added to an ethereal solution of phenylmagnesium bromide (40 ml, 3.01M diluted to 150 ml, Alfa. Inorganics) under nitrogen. The mixture was refluxed for 24 h after which the solution was evaporated to 25% volume and dry tetrahydrofuran (400 ml) added, followed by phenylmagnesium bromide (20 ml, 3.01 M). Refluxing was continued with stirring for 24 h.

To the cooled solution was added acetic acid (150 ml) and water (120 ml). Tetrahydrofuran was removed by distillation, after which the oily mixture was heated at reflux for 20 min, cooled, and poured into water (1500 ml). Ether extraction (3 × 400 ml) gave a solution which was washed with saturated $NaHCO_3$ solution, water, dried (Na_2SO_4) and evaporated. Chromatography of the yellow oil on silica gave the product in mixtures of hexane and ethyl acetate. Crystallization from methanol/water gave **3e** (2g., 28%, m.p. 173–178° - shrinks 120°) as a hydrate. IR ($CHCl_3$): 3420(w.br), 1646(s), 1604(m), 1585(s), 1210–1240(s), 1040(s), 699(m) cm^{-1}. (Found: C, 79.03; H, 8.71. Calc. for $C_{26}H_{32}O_2 \cdot H_2O$: C, 79.15; H, 8.69%.)

Acetate **3f**. Treatment of **3e** in the usual way with acetic anhydride/pyridine at room temp. for 24 h gave **3f**, m.p. 156–157°. *IR* ($CHCl_3$): 1730(*s*), 1640(*m*), 1602(*m*), 1595(*m*), 1210–1250(*s*), 1032(*s*) cm^{-1}. *NMR* 1.12(*s*, 3*H*); 2.02(*s*, 3*H*), 4.6(*br*, 1*H*), 5.4(*m*, 1H), 6.42(m, 1H), 7.3–7.8(5H) δ. (Found: C, 80.14; H, 8.22; O, 11.68. Calc. for $C_{28}H_{34}O_3$: C, 80.35; H, 8.19; O, 11.47%.)

General procedure for the addition of diphenylnitrile imines to 17-acetyl, benzoyl and cyano steroids. To a solution of the steroid (2.8 mmoles) and the aroyl chloride arylhydrazone (3.1 mmoles) in benzene (25 ml) was added triethylamine (10 mmoles) in benzene (3 ml) during 24 h at RT. Stirring was usually continued for a further 24 h although in most cases TLC indicated the reaction to be complete after 2–3 h. The reaction mixture was filtered to remove triethylamine hydrochloride, washed with water, dried and evaporated to give the crude product. In some cases chromatography on silicagel preceded recrystallization. In this way the following adducts were prepared:

4a, yellow needles (CH_3OH), m.p. 255–56°; 65%. IR (Nujol): 1728(s), 1712(s), 1598(s), 1490(s), 1250(s), 1030(s), 770(m), 748(s), 691(s) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.25(s, 3H, 18–CH_3), 1.85(s, 3H, 21–CH_3), 4.20(br, 1H, w/2 13 Hz, 16–H). UV (dioxan): 372 (ϵ, 15.040), 322 (ϵ, 11,460), 310 (ϵ, 10,880), 298 sh (8640), 246 (ϵ, 19,840) nm. CD (dioxan) 365 ($\Delta\epsilon$, +57.1), 318 (−64.1), 309 (−57.7), 242 (−26.9) nm. M^+ 550. (Found: C, 78.34; H, 7.70; N, 5.26; O, 8.85. Calc. for $C_{36}H_{42}N_2O_3$: C, 78.51, H, 7.69; N, 5.09; O, 8.72%.)

4b, cream needles (CH_2Cl_2/CH_3OH), m.p. 236–238°; 90%. IR (Nujol): 1730(s), 1708(s), 1600(m), 1580(w), 1495(m), 1240(s), 1030(s), 765(m), 755(s) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.22(s, 3H, 18–CH_3), 2.01(s, 6H, 3β-OAc, 21–CH_3), 4.6(br, 1H, 3α-H), 4.7(br, 1H, 16-H), 5.3(br, 1H, 6-H) δ. UV (dioxan) 364 (ϵ, 11,910), 310 (10,860), 300 sh (10,110), 246 (16860) nm. CD (dioxan): 254 ($\Delta\epsilon$, +55.8), 310 (−43.7), 248 (−16.6), nm. M^+ 584, 586 (~3/1) (Found: C, 74.05; H, 6.98; N, 4.80; O, 7.99; Cl, 6.02. Calc. for $C_{36}H_{41}ClN_2O_3$: C, 74.06; H, 6.88; N, 4.78; O, 8.20; Cl, 6.07%.)

4c, cream needles (CH_2Cl_2/CH_3OH), m.p. 245.5–247°, 85%. IR (Nujol): 1727(s), 1701(s), 1595(m), 1575(w), 1490(m), 1240(s), 1030(m), 765(m), 755(m), 700(w) cm^{-1}. NMR 0.98(s, 3H, 19–CH_3), 1.20(s, 3H, 18–CH_3), 1.98(s, 3H, 3β-OAc), 4.7(br, 1H, 16-H) δ. (Found: C, 68.66; H, 6.70; N, 4.34; Br, 12.71. Calc. for $C_{36}H_{41}N_2O_3Br$: C, 68.67; H, 6.56; N, 4.45; Br, 12.69%.)

4d, pale yellow plates (CH_2Cl_2/CH_3OH), m.p. 227–229°, 64%. IR (Nujol): 1730(s), 1720(sh.s), 1595(m), 1564(w), 1495(m), 1245(s), 1030(m), 780(m), 760(m), 685(m) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.22(s, 3H, 18–CH_3), 1.86(s, 3H, 21–CH_3), 2.01(s, 3H, 3β-OAc), 4.2(br, 1H, 16-H) δ. UV (dioxan): 376 (ϵ, 15,400), 324 (9260), 313 (8290), 229 sh. (6060), 251 (16,370) nm. CD (dioxan): 370 ($\Delta\epsilon$ + 46.0), 322 (−56.2), 313 (−52.2), 245 (−23.0), nm. M^+ 584, 586 (~3/1). (Found: C, 74.10; H, 7.11; N, 4.69; Cl, 5.88; O, 7.91. Calc. for $C_{36}H_{41}ClN_2O_3$: C, 74.06; H, 6.88; N, 4.78; Cl, 6.07; O, 8.20%.)

4e, pale yellow needles (CH_3OH/hexane), m.p. 203–205°, 44%. IR (Nujol): 1740(s), 1715(s), 1600(m), 1580(w), 1490(m), 1240(s), 1032(m), 830(m), 751(m), 692(w) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3,

1.23(s, 3H, 18–CH_3), 1.84(s, 3H, 21–CH_3), 2.00(s, 3H, 3β-OAc), 4.2(br, 1H, 16-H) δ. UV (dioxan): 371 (ε, 13,900), 322 (12,900), 310 (12,550), 252 (15,400), 244 (15,500) nm. CD (dioxan): 369 (Δε, +64.2), 322 (−73.8), 3.14 sh (−69.6), 248 (−26.0), nm. M^+ 584, 586 (~3/1). (Found: C, 74.11; H, 6.99; N, 4.88; Cl, 6.04; O, 8.30. Calc. for $C_{34}H_{41}ClN_2O_3$: C, 74.06; H, 6.88; N, 4.78; Cl, 6.07; O, 8.20%.)

4f, pale yellow needles (CH_3OH/hexane), m.p. 175–180°, 30%. IR (Nujol): 1730(s), 1710(s), 1600(m), 1580(w), 1496(s), 1250(s), 1030(m), 835(m), 749(m), 692(w) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.25(s, 3H, 18–CH_3), 1.83(s, 3H, 21–CH_3), 2.00(s, 3H, 3β-OAc), 4.2(br, 1H, 16-H) δ. UV (dioxan): 368 (ε, 14,040), 319 (13,510), 310 (14,180), 300 (12,450), 250 (19,080) nm. CD (dioxan): 365 (Δε, +51.1), 317 (−58.8) 310 (−53.6), 238 (−8.0), 224 (+10.4) nm. (Found: C, 76.61; H, 7.61; N, 4.67; O, 11.06. Calc. for $C_{37}H_{44}N_2O_4$: C, 76.52; H, 7.64; N, 4.82; O, 11.02%.)

4g, colorless needles (CH_3OH), m.p. 241–243°, 49%. IR (Nujol): (1730(s), 1700(s), 1582(m), 1560(w), 1480(s), 1252(s), 1235(s), 1107(m), 1042(m), 1030(m), 765(s), 755(s), 688(m) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.30(s, 3H, 18–CH_3), 2.00(s, 3H, 3β-OAc), 2.25(s, 3H, 21–CH_3), 4.20(br, 1H, 16-H) δ. UV (dioxan): 362 (ε, 18,310), 355 (17,710), 316 (20,035), 308 (17,605), 275 (9680), 235 (17,960) nm. CD (dioxan): 358 (Δε, +64.6), 314 (−90.5), 235 (+23.9) nm. M^+ 584,586 (~3/1). (Found: C, 73.68; H, 6.99; N, 4.92; Cl, 6.40; O, 8.23. Calc. for $C_{36}H_{41}ClN_2O_3$: C, 74.06; H, 6.88; N, 4.78; Cl, 6.07; O, 8.20%.)

4h, pale yellow needles (CH_3OH/hexane), m.p. 176–180°, 60%. IR ($CHCl_3$), 1726(s), 1710(s), 1592(s), 1568(w), 1490(s), 1250(s), 1030(m), 824(s), 690(w) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.20(s, 3H, 18–CH_3), 1.82(s, 3H, 21–CH_3), 2.00(s, 3H, 3β-OAc), 4.2(br, 1H, 16-H) δ. UV (dioxan): 372 (ε, 13,970), 323 (13,010), 312 (12,530), 252 (15,470), 245 (15,560) nm. CD (dioxan): 366 (Δε, +48.0), 320 (−55.0), 240 (−19.2), nm. (Found: C, 74.22; H, 7.05; N, 4.65; Cl, 6.05; O, 8.09. Calc. for $C_{36}H_{41}ClN_2O_3$: C, 74.06; H, 6.88; N, 4.78; Cl, 6.07; O, 8.20%.)

8a, yellow needles (CH_3OH/hexane), m.p. 268–71°, 54%. IR (KBr): 1730(s), 1662(s), 1595(s), 1492(s), 1242(s), 1025(s), 860(m), 765(s) 750(s), 690(s) cm^{-1}. NMR 1.00(s, 3H, 18–CH_3), 1.16(s, 3H, 18–CH_3), 1.98(s, 3H, 3β-OAc), 4.3(br, 1H, 16–H) δ. UV (dioxan): 396 (ε, 6120), 337 (13,890), 248 (23,540), 222 (13,900) nm. CD (dioxan): 400 (Δε, +52.9), 338 (−64.8), 295 (+20.6), 257 (−51.3), nm.

8b, amorphous powder (CH_2Cl_2/CH_3OH), no distinct m.p.: softens 130–170°. IR (KBr): 1735(s), 1680(s), 1595(s), 1580(w), 1500(s), 1240(s), 1035(s), 750(s), 695(s) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.16(s, 3H, 18–CH_3), 2.00(s, 3H, 3β-OAc), 4.72(br, 1H, 16-H) δ.

9a, colorless needles (CH_2Cl_2/CH_3OH), m.p. 270–275(d), 80%. IR (Nujol): 2230(w), 1729(s), 1598(s), 1583(w), 1493(s), 1251(s), 1038(m), 1022(m), 772(m), 758(s), 699(s) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.30(s, 3H, 18–CH_3), 1.98(s, 3H, 3β-OAc), 4.6(br, 1H, 16-H) δ. UV (dioxan): 340 (ε, 16,000), 293 (5445), 241 (17,740) nm. CD (dioxan): 326 (Δε, +21.2), 283 (−6.2), 235 (−26.7), nm. M^+, 533. (Found: C, 78.92; H, 7.50; N, 7.94. Calc. for $C_{35}H_{39}O_2N_3$: C, 78.76; H, 7.36; N, 7.87%.)

9b, colorless plates (CH_3OH/H_2O), m.p. 233–237°, 62%. IR (KBr): 2230(w), 1730(s), 1600(s), 1585(m), 1495(s), 1250(s), 1030(s), 768(s), 756(s), 695(s) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.28(s, 3H, 18–CH_3), 1.97(s, 3H, 3β-OAc), 2.62(s, 3H, Ar-CH_3), 4.56(br, 1H, 16-H) δ. (Found: C, 78.93; H, 7.56; N, 7.57; O, 5.95. Calc. for $C_{36}H_{41}O_2N_3$: C, 78.94; H, 7.55; N, 7.67; O, 5.84%).

9c, colorless plates (CH_2Cl_2/CH_3OH), m.p. 201–203°, 97%. IR (KBr): 2230(w), 1730(s), 1595(s), 1490(s), 1270(s), 1235(s), 1205(s), 1100(s), 1030(s), 835(m), 760(s), 755(s), 695(m) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.29(s, 3H, 18–CH_3), 2.00(s, 3H, 3β-OAc), 4.67(br, 1H, 16-H) δ. Found: C, 75.98; H, 6.90; N, 7.52; F, 3.26. Calc. for $C_{35}H_{38}FN_3O_2$: C, 76.20; H, 6.94; N, 7.62; F, 3.44%.)

9d, colorless needles (CH_2Cl_2/CH_3OH), m.p. 210–212°, 78%. IR (KBr): 2230(w), 1725(s), 1600(s), 1585(m), 1495(s), 1245(s), 1030(s), 765(s), 750(s), 695(s) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.28(s, 3H, 18–CH_3), 2.00(s, 3H, 3β-OAc), 4.96(br, 1H, 16-H) δ. (Found: C, 73.52; H, 6.79; N, 7.40; Cl, 6.15. Calc. for $C_{35}H_{38}ClN_3O_2$: C, 73.99; H, 6.74; N, 7.40; Cl, 6.24%.)

9e, colorless needles (CH_2Cl_2/CH_3OH), m.p. 238–240°, 38%. IR (KBr): 2238(w). 1730(s), 1600(s), 1585(sh.m), 1493(s), 1240(s), 1023(s), 760(s), 750(s), 694(m) cm^{-1}. NMR 1.00(s, 3H, 19–CH_3), 1.29(s, 3H, 18–CH_3), 2.00(s, 3H, 3β-OAc), 4.94(br, 1H, 16-H), δ. (Found: C, 68.41; H, 6.36; N, 6.96; Br, 12.77. Calc. for $C_{35}H_{38}N_3O_2Br$: C, 68.62; H, 6.25; N, 6.86; Br, 13.04%.)

Hydrogenation of 3β-Acetoxypregna-5-en-20-ono-[16α,17α-d]-1',3'-diphenyl-2'-pyrazoline **4a**. The steroid, **4a**, (500 mg) in acetic acid (50 ml) was shaken in an atmosphere of hydrogen with platinum oxide (300 mg). After 24 h absorption was complete and the mixture was filtered, evaporated and the residue dissolved in methanol and filtered through silicagel. Evaporation gave a gel which slowly changed to a crystalline form. The product 7 was pure by TLC and NMR assays. Yield 235 mg, m.p. behavior - shrinks to glass 140–150°. IR ($CHCl_3$): 1725(s), 1695(s), 1210–1260(s), 1025(m) cm^{-1}. NMR 0.71(s. 3H, 18–CH_3), 0.94(s, 3H, 19–CH_3), 2.03(s, 3H, 3β-OAc), 2.17(s, 3H, 21–CH_3), 3.57(m, 1H, 16β-H), 6.06(br. s, w/2 5.5 Hz, 3α-H) δ. MS: M^+564 (5), 521 (M^+-43, 100) *m/e*. (Found: C, 76.34, H, 10.06; N, 4.96. Calc. for $C_{36}H_{56}N_2O_3$: C, 76.48; H, 9.99; N, 4.96%.)

3β-Acetoxy-17,17-dimethoxyandrost-5-ene **14**. A solution of 3β-acetoxyandrost-5-en-17-one (**3a**, 25.0g, 76.5 mmole, Searle Chemical Co.) in methanol (500 ml) was treated with trimethylorthoformate (25 ml, 325 mmole) and conc. sulfuric acid (5 drops). The precipitate formed by refluxing for 10 min was collected after cooling and treating with pyridine (15 ml). Recrystallization from CH_2Cl_2/CH_3OH containing a trace of pyridine gave the product, **14**, as colorless microcrystals, m.p. 148–149°. IR 2842(m), 1730(s), 1250(br, s), 1155(s), 1035(s) cm^{-1}. NMR 0.88(s. 3H, 18–CH_3), 1.02(s, 3H, 19–CH_3), 2.02(s, 3H, 3β-OAc), 3.25(s, 6H, OCH_3) δ. This compound was used without further purification in the next step.

3β-Acetoxy-17-methoxyandrost-5,16-diene **3d**. 3β-Acetoxy-17,17-dimethoxyandrost-5-ene (14.3g, 8 mmole) was heated at 220° with stirring under nitrogen for 24 h in the presence of crushed glass.[21] The cooled melt was dissolved in chloroform, treated with Norit, and the solution filtered and evaporated to yield a yellow oil, which was filtered through alumina (Act. I) in hexane. Recrystallization of the product from hexane containing a trace of pyridine afforded **3d**, 2.0g, 73%, m.p. 148–149°. IR ($CHCl_3$): 2842(m), 1730(s), 1629(m), 1235(br, s), 1156(m), 1115(m), 1030(s) cm^{-1}. NMR 0.89(s, 3H, 18–CH_3), 1.02(s, 3H, 19–CH_3), 2.00(s, 3H, 3β-OAc), 3.56(s, 3H, OCH_3), 4.36(br. 1H, 16-H). δ. (Found: C, 76.44; H, 9.44; O, 13.95. Calc. for $C_{22}H_{31}O_3$: C, 76.70; H, 9.36; O, 13.93%.)

3β-Acetoxy-17β-methoxyandrost-5-eno-[16α,17α-d]-1',3'-diphenyl-2'-pyrazoline **8c**. A solution of triethylamine (5g, 49.5 mmole) in benzene (10 ml) was added dropwise with stirring to a solution of **3d** (1.0g, 2.90 mmole) and benzoyl chloride phenylhydrazone[24] (1.0g, 4.33 mmole, m.p. 127–128°) in refluxing benzene (250 ml). The process was repeated again after another 48 h. After a further 24 h triethylamine (20g) was added and reflux continued for 24 h. The red mixture was filtered, washed with water, dried (Na_2SO_4), filtered and evaporated to yield a gum which was chromatographed on silicagel. Benzene/1% $CHCl_3$ gave a gum which was recrystallized from CH_2Cl_2/CH_3OH to give **8c**, 420 mg, 27%, colorless needles, m.p. 206–208°/250–252°. IR (KBr): 2840(m), 1736(s), 1570(w), 1495(s), 1320(s), 1250(s), 1126(s), 1100(s), 1060(s), 770(s), 745(s), 690(s) cm^{-1}. NMR 1.00 (s, 3H, 19–CH_3), 1.15(s, 3H, 18–CH_3), 2.01 (s, 3H, 3β-OAc), 3.09 (s, 3H, 17β-OCH_3), 3.84 (br, 1H, 16-H) δ. UV (dioxan): 344 (ε, 24,130), 304 (7380), 250 (18,750), 240 sh. (17,790) nm. CD (dioxan): 339 (Δε, +9.1), 290 (−10.5), 242 (−26.7) nm. M^+ 538. (Found: C, 78.42: H, 7.78: N, 5.28; O, 8.67. Calc. for $C_{35}H_{42}N_2O_3$: C, 78.03; H, 7.86; N, 5.20; O, 8.91%.)

Pyrolysis of 3β-acetoxy-17β-methoxyandrost-5-eno[16α,17α-d]-1',3'-diphenyl-2'-pyrazoline **8c**. (A) (300°) Compound **8c** (100 mg) was heated at 300°under nitrogen for 3 h. The crude product was chromatographed on basic alumina (Act I) to give androst-3,5-dieno-[16,17-d]-1',3'-diphenylpyrazole **15** in hexane/10% $CHCl_3$. Recrystallization from hexane/benzene gave needles (50 mg, 61%), m.p. 142–150°/188–190°. IR (KBr) 3035(m), 1601(s), 1505(s), 1480(m), 775 sh(s), 762(s), 690(s), 670(s) cm^{-1}. (Found: C, 86.09; H, 8.04; N, 6.04. Calc. for $C_{32}H_{42}N_2$: C, 86.05; H, 7.67; N, 6.27%.) (B) (250°) Compound **8c** (100 mg) was heated at 260° for 1 h. Recrystallization from CH_2Cl_2/CH_3OH gave

colorless needles of 3β-acetoxyandrost-5-eno[16,17-d]1',3'-diphenylpyrazole **10a**, m.p. 250–252°, 80 mg, 90%. IR (KBr): 1738(s), 1599(m), 1505(s), 1250(s), 1030(s), 768(s), 695(s), 670(s) cm^{-1}. NMR 1.07(s, 3H, 18–CH_3), 1.11(s, 3H, 19–CH_3), 2.01(s, 3H, 3β-OAc). δ. UV (dioxan): 290 sh (ε, 19170), 282 sh (23580), 276 (24820), 235 (15720), 220 (21180) nm. $[\alpha]_{360}^{25}$ − 338° (C = 2, $CHCl_3$). M^+ 506. (Found: C, 80.22; H, 7.68; N, 5.50; O, 6.32. Calc. for $C_{34}H_{38}N_2O_2$: C, 80.57; H, 7.56; N, 5.53; O, 6.32%.)

Pyrolysis of 3β-acetoxy-17β-cyanoandrost-5-eno-[16α,17α-d]-1',3'-diphenyl-2'-pyrazoline **9a**. Compound **9a** (40 mg) was heated under nitrogen for 1 h at 290–300° until gas evolution ceased. Recrystallization from CH_2Cl_2/CH_3OH gave pyrazole **10a**, identical in all respects with the sample prepared from the 17β-methoxy analog.

3β-Acetoxy-17-benzoylandrost-5,16-diene phenylhydrazone **11**. To **3f** (0.7g, 1.67 mmole) in ethanol (20 ml) was added water (3 ml), acetic acid (6 ml) and phenylhydrazine (3 ml). The solution was brought to reflux followed by the addition of conc. H_2SO_4 (2 drops) and water to dissolve precipitated solid. After 2 h reflux the solution was cooled, water added and the resulting solid collected and recrystallized from $EtOH/H_2O$ as fine, yellow needles, 0.3 g, 35%, m.p. 172–175°. IR (KBr): 1735(s), 1603(s), 1550(w), 1503(s), 1250(s), 1035(m), 745(m), 690(m) cm^{-1}. NMR 1.11(s, 3H, 19–CH_3), 1.17(s, 3H, 18–CH_3), 2.03(s, 3H, 3β-OAc), 5.4(br, 2H, 6-H, 16-H) δ. (Found: C, 80.21; H, 8.10; N, 5.50; O, 6.23. Calc. for $C_{34}H_{40}N_2$: C, 80.28; H, 7.93; N, 5.51; O, 6.29%.)

Preparation of 3β-acetoxyandrost-5-eno[17α,16α-d]-1',3'-diphenyl-2-pyrazoline **12b**. (A) Compound **11** (140 ml) was refluxed in ethanol (10 ml) containing conc. HCl for 48 h. Cooling yielded **12a** as green crystals, m.p. 270–273°, 100 mg. IR (KBr): 3582(m), 1600(s), 1552(m), 1496(s), 1340(s), 1290(m), 1110(m), 1046(s), 692(s) cm^{-1}. NMR 0.97(s, 3H, 19–CH_3), 1.17(s, 3H, 18–CH_3), 1.54(s, 1H, 3β-OH), 3.80, 3.99 (d, J = 10.5 Hz, 1H, 17β-H), 7.74 (dd, J = 10.5, 5.0 Hz, 1H, 16β-*H*) δ. UV 360 (ε, 22,070), 316 sh (8430), 255 (14,310), 244 sh (13,090) nm. CD (dioxan): 377 (Δε, −2.2), 336 (−7.7), 253 (−10.3), 237 (+7.1) nm. M^+ 466. (Found: C, 81.71; H, 8.22; N, 6.22; O, 3.76. Calc. for $C_{32}H_{38}N_2O$: C, 82.36; H, 8.21; N, 6.00; O, 3.43%.)

Acetylation of **12a** (Ac_2O/pyridine, R.T., 24 h) gave **12b**, identical with the sample formed by method B. (B) Compound **11** (1.1g) was refluxed in ethanol (35 ml) containing conc. HCl (10 drops). After 10 min the product began to separate from solution. Cooling, filtration and recrystallization (CH_2Cl_2/CH_3OH) gave **12b** as pale yellow needles, 460 mg, 42%, m.p. 252–254°. IR (KBr): 1733(s), 1600(s), 1504(s), 1497(s), 1250(s), 1035(m), 759(s), 749(s), 690(s) cm^{-1}. NMR 0.97(s, 3H, 19–CH_3), 1.14(s, 3H, 18–CH_3), 1.99(s, 3H, 3βOAc), 3.76, 3.94 (d, J = 10.5 Hz, 1H, 17β-H), 4.3–4.8 (br, 2H, 3α-H, 16β-H). δ. (Found: C, 80.34; H, 7.92; N, 5.35; O, 6.24. Calc. for $C_{34}H_{40}N_2O_2$: C, 80.28; H, 7.93; N, 5.51; O, 6.29%.)

Preparation of 3β-acetoxyandrost-5-eno-[17,16-d]-1',3'-diphenylpyrazole **13**. A solution of **12b** (100 mg, 0.2 mmole) in dry benzene (20 ml) was refluxed under nitrogen with dichlorodicyano benzoquinone (57 mg, 0.25 mmole) for 24 h. The mixture was filtered and the precipitate washed with benzene. The combined filtrates were chromatographed on basic alumina (Act. I) in benzene. Recrystallization from CH_3OH/H_2O furnished **13** as fine colorless needles, 60 mg, 61%, m.p. 245–246°. IR (KBr): 1739(s), 1605(m), 1532(w), 1510(s), 1250(s), 1100(w), 1032(s), 760(s), 700(m), 691(m) cm^{-1}. NMR 1.11(s, 3H, 19–CH_3), 1.14(s, 3H, 18–CH_3), 2.03(s, 3H, 3β-OAc), δ. UV (dioxan): 285 (ε, 22,750), 235 (11,940), 222 (17,850) nm. $[\alpha]_{360}^{25}$ −278° (C = 2, $CHCl_3$). (Found: C, 80.53; H, 7.51; N, 5.52; O, 6.34. Calc. for $C_{34}H_{38}O_2N_2$: C, 80.60; H, 7.56; N, 5.53; O, 6.32%.)

Addition of diphenylnitrilimine to 3β,17-diacetoxyandrost-5,16-diene **3c**. Triethylamine (2.0 g, 19.80 mmole) in benzene (15 ml) was added to a solution of **3c** (1.0 g, 2.7 mmole) and benzoyl chloride phenylhydrazone (3.00 g, 13.0 mmole) in benzene (30 ml) during 25 min. After 48 h the dark brown solution was washed with water, dried (Na_2SO_4) and evaporated. Addition of methanol gave a pale pink solid. Crystallization from methanol gave 3β-acetoxyandrost-5-eno-[16,17-d]-1',3'-diphenylpyrazole **10a** as colorless needles, m.p. 251.5–252.5°, 0.35 g, 26%, identical with the sample prepared earlier.

3β - Acteoxyandrost - 5 - eno - [16,17-d] - 1' - phenyl - 3' - p - chlorophenyl-pyrazole **10b**. This compound was prepared by the method used for **10a**. It crystallized from methanol as colorless needles, 5%, m.p. 193–195°. IR (nujol): 1735(s), 1600(w), 1505(w), 1250(s), 1140(w), 1095(w), 1030(m), 832(m), 768(m), 695(w) cm^{-1}. NMR 1.08(s, 3H, 19–CH_3), 1.12(s, 3H, 18–CH_3), 2.03(s, 3H, 3β-OAc), 7.38 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H) (*p*-substd benzene) δ. (Found: C, 75.50; H, 6.72; N, 5.19; O, 5.88; Cl, 6.73. Calc. for $C_{34}H_{37}ClN_2O_2$: C, 75.60; H, 6.72; N, 5.18; O, 5.92; Cl, 6.56%.)

3β-Acetoxyandrost-5-eno-[16,17-d]-1'-p-chlorophenyl-3'-phenylpyrazole **10c**. This compound synthesized by the method used for **10a** crystallized from methanol as colorless needles, 17%, m.p. 229–230°. IR (nujol): 1732(s), 1595(w), 1500(s), 1250(s), 1090(w), 1032(m), 836(m), 771(w), 692(w) cm^{-1}. NMR 1.08(s, 3H, 19–CH_3), 1.10(s, 3H, 18–CH_3), 7.38 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H) (*p*-substd benzene) δ. (Found: C, 75.45; H, 6.95; N, 5.00; O, 5.94; Cl, 6.42. Calc. for $C_{34}H_{37}ClN_2O_2$: C, 75.60; H, 6.72; N, 5.18; O, 5.92; Cl, 6.56%.)

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