Synthesis of steroidal D-ring fused pyrazolines: Study of regiochemistry of addition

Brian Green and Kueiying Sheu

Department of Chemistry, University of Maine, Orono, Maine

*The addition of diphenylnitrilimine and C-o-chlorodiphenylnitrilimine to 3β-hydroxyandrost-5,16-diene (**3b**) produced a 1/1 ratio of regioisomeric, 1,3-diaryl-2-pyrazolines (**6a**, **7a** and **6b**, **7b**), whereas the addition of N-o-chlorodiphenylnitrilimine gave a 5/1 ratio in favor of the [17α,16α-d] regioisomer (**7c**). To further delineate the factors governing the regiochemistry of addition of diphenylnitrilimines to steroid 16-enes, additions were carried out on 16-acetyl-5α-androst-16-ene (**5b**) and 1-acetylcyclopentene (**10**).*
(*Steroids* **59**:479–484, 1994)

Keywords: D-ring addition; diarylpyrazolines; diphenylnitrilimines; regiochemistry

Introduction

With the initial goal of producing steroids with anticancer activity, we have been interested for some time in the synthesis of steroidal fused-ring heterocycles[1,2] by the application of the 1,3-dipolar addition reaction to activated double bonds.[3] In earlier work[2] it was found that addition of diphenylnitrilimines to 17-substituted-16-androstenes gave [16α,17α-d]-2′-pyrazolines (**1a–1c**) as the exclusive regioisomers, regardless of the electronic nature of the 17-substituent (Figure 1).

To gain further information on the factors controlling the regiochemistry of this reaction, 3β-hydroxyandrost-5,16-diene (**3b**) and 16-acetyl-5α-androst-16-ene (**5b**) were chosen as dipolarophiles. In the first case it was of interest to discover whether addition would occur to an unactivated double bond and if so whether any regioselectivity would be observed. In the second case the goal was to discover whether an acetyl group at the 16-position would lead, by analogy to our previous work, to the exclusive formation of the [17α,16α-d] regioisomer.

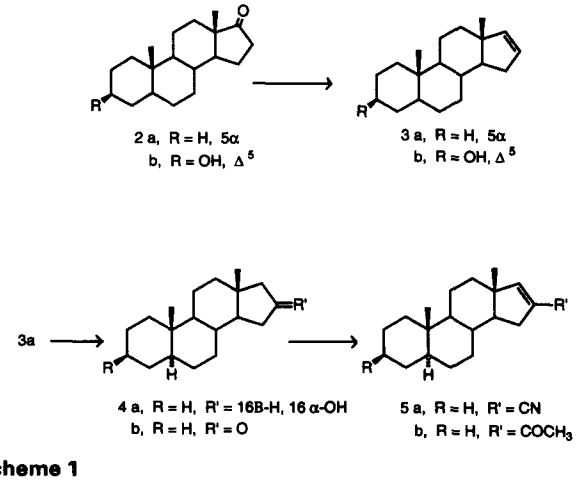
To ascertain whether the steroidal skeleton was influencing the regiochemical outcome, additions to the model compound 1-acetylcyclopentene (**10**) were studied.

Experimental

Melting points (Thomas-Hoover) are uncorrected. IR spectra were obtained on a Perkin-Elmer 457 instrument. ^{1}H NMR spectra ($CDCl_3$) were recorded on a Varian XL-200 instrument. Low resolution mass spectra were taken on a Hewlett-Packard 5985 system and high resolution mass spectra were run on a CEC 21-110 instrument at the Massachusetts Institute of Technology. Silica gel HF254 (E. Merck) was used for thin-layer chromatography (TLC) and vacuum liquid chromatography (VLC)[4] analysis. HPLC separations were achieved on a Waters Associates M-6000A instrument equipped with a Micromeritics 786 detector. Elemental analyses were provided by W. Galbraith Laboratories (Knoxville, TN, USA). Organic extracts were dried with Na_2SO_4.

5α-Androstan-16α-ol (4a)

To 5α-androst-16-ene (**3a**)[8] (22.7 g, 88 mmol) in tetrahydrofuran (150 mL) was added dropwise a solution of 9-borabicyclononane in tetrahydrofuran (210 mL, 0.5 M) at



Scheme 1

Address reprint requests to Dr. Brian Green, 387 Aubert Hall, University of Maine, Orono, ME, 04469, USA.
Received August 4, 1993; accepted February 16, 1994.

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room temperature under nitrogen. Stirring was continued for 2 h at 30°C, followed by the addition of hydrogen peroxide (42 mL, 30%) and aqueous NaOH (21 mL, 2 N). After 1 h at 50°C the solution was cooled to room temperature and extracted with ether. Drying and evaporation yielded a product which was chromatographed on silica gel in hexane/chloroform to give 21 g of crude product. Recrystallization from hexane gave **4a** (14.4 g, 59%), m.p. 156–158°C (lit.[5] 157°C): ^{1}H NMR 0.69 (s, 3H, 19-methyl), 0.78 (s, 3H, 18-methyl), 4.49 (br, 1H, 16-H) ppm.

5α-Androstan-16-one (4b)

A solution of sodium dichromate dihydrate (5 g, 16.8 mmol) and sulfuric acid (3.75 mL, conc.) in water (15 mL) was added dropwise at 25 C to a solution of 5α-androstan-16α-ol (**4a**) (13.9 g, 50.4 mmol) in tetrahydrofuran/ether (500 mL, 1/1). After 2 h of stirring the upper layer was separated and extracted with 2 portions of ether. Washing successively with aqueous $NaHCO_3$ and water, drying and evaporating gave **4b** (13.8 g, 100%), m.p. 105–107°C (lit.[5] 107 C): ^{1}H NMR 0.80 (s, 3H, 19-methyl), 0.85 (s, 3H, 18-methyl) ppm.

16-Cyano-5α-androst-16-ene (5a)

To a solution of 5α-androstan-16-one (**4b**) (13.5 g, 49.3 mmol) and KCN (102 g, 1.57 mmol) in ethanol (500 mL) was added acetic acid (110 mL) with stirring during 1 h. After 2 h at room temperature the mixture was diluted with water (800 mL). The precipitate was collected by filtration, washed with 10% acetic acid, then water, and dried to give a mixture of epimeric cyanohydrins (13.4 g): IR (KBr) 3470, 3370 (hydroxyl), 2242 (nitrile) cm^{-1}. The cyanohydrin mixture (12.9 g, 42.9 mmol) was refluxed for 8 h in pyridine containing phosphorus oxychloride (21 mL, 225 mmol). After standing overnight at room temperature the dark solution was poured with vigorous stirring into a mixture of ice and HCl (1 L, 3 M). After 15 min the precipitate was collected by filtration, washed with dilute HCl, and then with water. Recrystallization from acetone/water (Norit) gave **5a** as needles (6.7 g, 55%), m.p. 131.5–133.5°C: ^{1}H NMR 0.83 (s, 6H, 18,19-methyls), 6.76 (br, 1H, 17-H) ppm: IR (KBr) 2231 (nitrile) cm^{-1}. High resolution mass spectroscopy (MS) for $C_{20}H_{29}N$: Calculated 283.23000. Found: 283.23245 mu.

16-Acetyl-5α-androst-16-ene (5b)

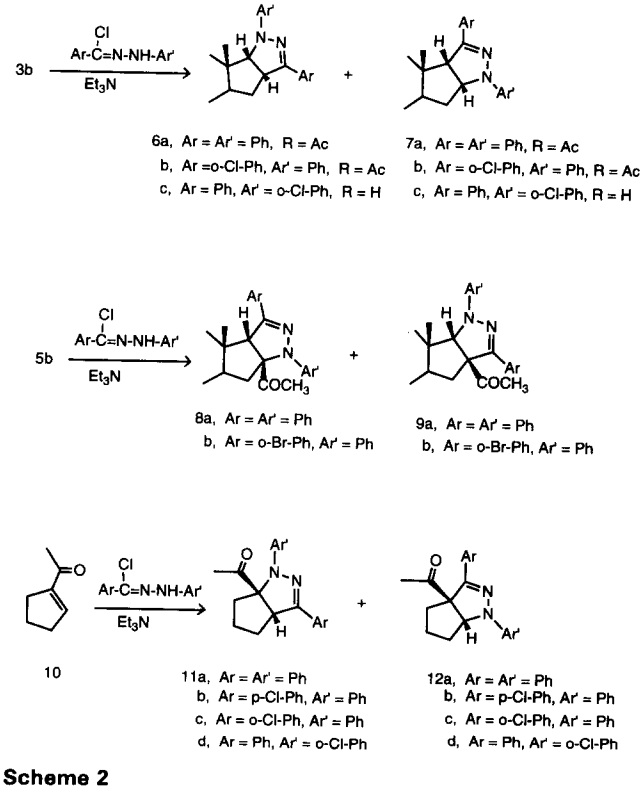
A solution of methylmagnesium bromide in ether (51 mL, 3.2 M, 163 mmol) was added dropwise to 16-cyano-5α-androst-16-ene (**5a**) (6.7 g, 23.7 mmol) in ether (250 mL). Refluxing was continued for 12 h, after which the cooled solution was added during 1.5 h to a stirred solution of acetic acid (500 mL) in water (500 mL). After 1 h on the steam bath the mixture was cooled and treated with HCl (150 mL, 6 M). The product was collected by filtration, dissolved in ether, and washed with 5% aqueous $NaHCO_3$. Drying and evaporation gave a cream colored product (7.6 g) which was recrystallized from pentane and then methanol to yield **5b** (4.3 g, 68%), m.p. 162–163.5°C: ^{1}H NMR 0.92 (s, 3H, 19-methyl), 0.94 (s, 3H, 18-methyl), 2.37 (s, 3H, acetyl), 6.89 (br, 1H, 17-H) ppm: IR (neat) 1665 (ketone) cm^{-1}. High resolution MS for $C_{21}H_{30}O$: Calculated 300.2453. Found: 300.2446 mu.

Addition of diphenylnitrilimine to 16-acetyl-5α-androst-16-ene (5b)

To a solution of 16-acetyl-5α-androst-16-ene (**5b**; 0.5 g, 1.76 mmol) and benzoyl chloride phenylhydrazone (0.45 g, 1.94 mmol) in benzene (40 mL) was added triethylamine (0.7 g) in benzene (10 mL). After 48 h with stirring the benzene was removed by evaporation and the brown residue crystallized from methanol/chloroform to give pale yellow crystals (0.61 g, 74%) of a mixture of **8a** and **9a** in a ratio of 6/1. IR (KBr) 1715 (ketone), 1495, 1598 (diphenylpyrazoline) cm^{-1}. A portion of the mixture was almost completely separated by HPLC in 6% water/methanol on a reverse phase column (Whatman, Partisil PXS 10/25, ODS-2). 16β-Acetyl-5α-androstano-[17α,16α-d]-1,3-diphenyl-2-pyrazoline (**8a**) eluted first: MS 494 (M$^+$, 4), 451 (11), 233 (100), 217 (10), 130 (12), 91 (12), 77 (11), 43 (18) mu: ^{1}H NMR 0.73 (s, 3H, 19-methyl), 1.01 (s, 3H, 18-methyl), 2.02 (s, 3H, acetyl), 2.50 (t, 1H, 15β-H), 3.70 (s, 1H, 17β-H) ppm. The minor isomer, 16β-acetyl-5α-androstano-[16α,17α-d]-1,3-diphenyl-2-pyrazoline (**9a**), showed the following spectral properties: MS 494 (M$^+$, 12) 451 (2), 313 (15), 233 (100), 183 (9), 167 (11), 149 (27), 130 (29), 109 (12), 91 (37), 43 (35) mu: ^{1}H NMR 0.75 (s, 3H, 19-methyl), 0.92 (s, 3H, 18-methyl), 2.05 (s, 3H, acetyl), 4.25 (s, 1H, 17β-H) ppm.

Addition of C-o-bromodiphenylnitrilimine to 16-acetyl-5α-androst-16-ene (5b)

The reaction was carried out on 0.5 g of **5b** using *o*-bromobenzoyl chloride phenylhydrazone exactly as described for diphenylnitrilimine to give a 6/1 mixture of **8b**, **9b** (0.81 g, 85%). A small sample was separated by preparative TLC to give **8b** as pale yellow crystals, m.p. 136–139°C (d): IR (KBr) 1715 (ketone), 1598, 1500 diphenylpyrazoline) cm^{-1}: ^{1}H NMR 0.73 (s, 3H, 19-methyl), 0.92 (s, 3H, 18-methyl), 2.14 (s, 3H, acetyl), 2.50 (t, 1H, 15β-H) 4.39 (s, 1H, 17β-H) ppm: MS 574,572 (M$^+$, 18), 531,529 (55), 313 (100), 232 (26), 217 (22), 130 (26), 95 (28), 67 (35), 43 (59) mu. High resolution MS for $C_{34}H_{41}N_2OBr$: Calculated 574.2411. Found: 574.2382 mu. The minor isomer **9b** showed the following ^{1}H NMR data: 0.75



Scheme 2

(s, 3H, 19-methyl); 0.90 (s, 3H, 18-methyl); 2.13 (s, 3H, acetyl); 4.41 (s, 17β-H) ppm.

Addition of diphenylnitrilimine to 3β-hydroxyandrost-5,16-diene (3b)

The reaction was carried out on **3b** (0.5 g, 1.84 mmol) using benzoyl chloride phenylhydrazone (0.64 g, 2.76 mmol) and triethylamine (10 g, 10 mmol) in benzene (25 mL). After 48 h at RT a further 0.5 g (2.16 mmol) of the phenylhydrazone was added. Workup was carried out after 6 days to give a dark brown gum which was flash-chromatographed on TLC grade silicagel to give 0.83 g of material which was acetylated overnight in pyridine (9 mL) and acetic anhydride (3 mL) at room temperature. Workup in the usual way gave 0.69 g (74%) of a 1/1 mixture of **6a** and **7a** which was crystallized from hexane/ethyl acetate and then ethyl acetate/methanol as pale cream needles, m.p. 255–258°C. Repeated crystallization and chromatography failed to separate the regioisomers. IR (nujol) 1730 (acetate), 1600, 1492, 1501 (diphenylpyrazoline) cm^{-1}: ^1H NMR (**6a**) 1.01 (s, 3H, 18 or 19 methyl), 1.06 (s, 3H, 18 or 19 methyl); 2.01 (s, 3H, acetate); 4.28 (d, J = 9.5 Hz, 1H, 17β-H); 4.16 (m, 16β-H); (**7a**) 0.99 (s, 3H, 18 or 19 methyl); 1.08 (s, 3H, 18 or 19 methyl); 2.01 (s, 3H, acetate); 3.91 (d, J = 10.5 Hz, 1H, 17β-H); 4.71 (dd, J = 10.5, 5.5 Hz, 1H, 16β-H) ppm: MS 508 (M^+, 100), 448 (10), 233 (42), 221 (56), 220 (78), 219 (33) mu: Calculated for $C_{34}H_{40}N_2O_2$: C, 80.27; H, 7.92; N, 5.51. Found: C, 80.14; H, 8.03; N, 5.40.

Addition of C-o-chlorodiphenylnitrilimine to 3β-hydroxyandrost-5,16-diene (3b)

The reaction was carried out on **3b** (0.5 g; 1.84 mmol) using *o*-chlorobenzoyl chloride phenylhydrazone (0.73 g; 2.76 mmol) and triethylamine (10 g; 10 mmol) in benzene (30 mL). A deep red color developed immediately, turning to almost black after 5 h. A further 0.5 g of the hydrazone was added after 24 h. Workup was effected after 48 h to yield a dark gum which was subjected to VLC[10] in 3/2 ethyl acetate/hexane. The fractions containing the pyrazolines were combined (822 mg, 87%) and acetylated overnight in acetic anhydride/pyridine to give a brown gum (809 mg) containing a 1/1 mixture (NMR) of **6b** and **7b**. Crystallization from ethanol gave material of the same composition, m.p. 180–185°C: IR (nujol) 1732 (acetate), 1601, 1500 (diphenylpyrazoline), 1250, 1035 (acetate) cm^{-1}: MS 544 (40), 542 (100), 482 (11), 270 (13), 269 (32), 268 (37), 267 (76) mu: ^1H NMR (**6b**) 1.00 (s, 3H, 18 or 19 methyl); 1.03 (s, 3H, 18 or 19 methyl) 4.28 (d, J = 10.2 Hz, 1H, 17β-H); 4.55 (m, 1H, 16β-H): (**7b**) 0.98 (s, 3H, 18 or 19 methyl), 1.02 (s, 3H, 18 or 19 methyl); 2.02 (s, 3H, acetate); 4.45 (d, J = 10.7 Hz, 1H, 17β-H); 4.78 (dd, J = 10.7, 6.7 Hz, 1H, 16β-H) ppm: Calculated for $C_{34}H_{39}N_2O_2Cl$: C, 75.18, H, 7.24; N, 5.16. Found: C, 75.19; H, 7.51; N, 5.12.

Addition of N-o-chlorodiphenylnitrilimine to 3β-hydroxyandrost-5,16-diene (3b)

Triethylamine (10 g, 10 mmol) was added over 8 h to a solution of **3b** (0.5 g, 1.84 mmol) and benzoyl chloride 2-chlorophenylhydrazone (0.73 g, 2.76 mmol) in benzene (30 mL). TLC analysis showed very slow conversion to products at room temperature. Portions of the hydrazone (0.5 g) were added after 24 h and again after 72 h at which time the temperature was increased to 70°C and kept there for 24 h. Workup in the usual way gave a black tar which was subjected to 3 successive VLC[4] separations in 1/1 ethyl acetate/hexane to give a 5/1 mixture of **7c**/**6c** (230 mg, 25%) from which **7c** could be isolated by repeated crystallization from methylene chloride/hexane and then ethanol as needles, m.p. 236–240°C: IR (nojul) 3300 (br. hydroxyl), 1585, 1480 (diphenylpyrazoline) cm^{-1}: MS 502 (M^+, 37); 500 (M^+, 100); 268 (30); 257 (22); 256 (36); 255 (66); 254 (77); 219 (29) mu: ^1H NMR 0.94 (s, 3H, 18 or 19 methyl); 1.05 (s, 3H, 18 or 19 methyl); 3.86 (d, J = 10.2 Hz, 1H, 17β-H); 5.33 (dd, J = 10.2, 5.6 Hz, 1H, 16β-H) ppm: Calculated for $C_{32}H_{37}N_2OCl$: C, 76.70; H, 7.44; N, 5.59. Found: C, 76.63; H, 7.49; N, 5.66. ^1H NMR data for minor regioisomer **6c**: 0.95 (s, 3H, 18 or 19 methyl); 0.99 (s, 3H, 18 or 19 methyl); 4.34 (m, 1H, 16β-H); 4.74 (d, J = 10.2 Hz, 1H, 17β-H) ppm.

General procedure for the addition of diphenylnitrilimines to 1-acetylcyclopentene (10)

To a solution of 1-acetylcyclopentene (**10**) (1.0 g, 9.09 nmol) and the benzoyl chloride phenylhydrazone (10.0 mmol) in benzene (80 mL) was added triethylamine (3.25 g, 32.2 mmol) in benzene (30 mL). After 48 h with stirring at room temperature the benzene was removed under reduced pressure and the residue recrystallized. The following results were obtained by this procedure.

Addition of diphenylnitrilimine

Crystallization from methanol gave yellow needles of (±)-cis-1-acetyl-[2,1-d]-cyclopentano-1,3-diphenyl-2-pyrazoline (**11a**; 1.67 g, 60%), m.p. 125–126°C: IR (KBr) 1715 (ketone), 1600, 1492 (diphenylpyrazoline) cm^{-1}: ^1H NMR 2.07 (s, 3H, acetyl), 4.02 (br, 1H, 4-H) ppm: MS 304 (M^+, 13), 262 (21), 261 (100), 130 (7), 77 (10), 43 (4) mu. Calculated for $C_{20}H_{20}N_2O$: C, 78.94; H, 6.62; N, 9.26. Found: C, 78.69; H, 6.71; N, 9.18%. A trace of the regioisomer (**12a**) was observed in the mother liquor: ^1H NMR 2.0 (s, 3H, acetyl), 4.8 (t, br, 1H, 4-H).

Addition of C-p-chlorodiphenylnitrilimine

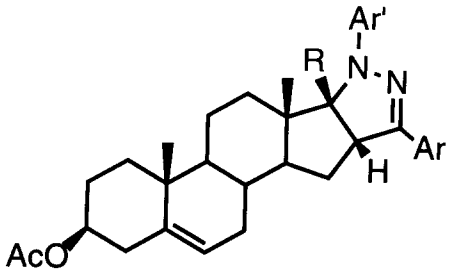
Crystallization from methanol yielded yellow crystals of (±)-cis-1-acetyl-[2,1-d]-cyclopentano-1-phenyl-3-(4-chlorophenyl)-2-pyrazoline (**11b**; 1.6 g, 52%), m.p. 126–128°C: IR (KBr) 1710 (ketone) 1595, 1490 (diphenylpyrazoline) cm^{-1}: ^1H NMR 2.05 (s, 3H, acetyl), 4.0 (br, 1H, 4-H) ppm: MS 340 (5), 338 (M^+, 15), 297 (35), 295 (100), 111 (5), 77 (5), 43 (7) mu. Calculated for $C_{20}H_{19}N_2OCl$: C, 70.92; H, 5.65; N, 8.27; Cl, 10.47. Found: C, 70.90; H, 5.73; N, 8.29; Cl, 10.62%. A trace of the regioisomer (**12b**) was detected in the mother liquor. ^1H NMR 4.62 (t, br, 1H, 4-H).

Addition of C-o-chlorodiphenylnitrilimine

Crystallization from methanol gave yellow needles of (±)-cis-1-acetyl-[2,1-d]-cyclopentano-1-phenyl-3-(2-chlorophenyl)-2-pyrazoline (**11c**) (1.6 g, 52%), m.p. 101–104°C: IR (KBr) 1712 (ketone), 1600, 1500 cm^{-1}: ^1H NMR 2.21 (s, 3H, acetyl), 4.49 (br, 1H, 4-H): MS 340 (4), 338 (M^+, 11), 297 (34), 295 (100), 130 (8), 77 (11), 43 (8) mu. Calculated for $C_{20}H_{19}N_2OCl$: C, 70.92; H, 5.65; N, 8.27; Cl, 10.47. Found: C, 70.83; H, 5.76; N, 8.29; Cl, 10.42.

Addition of N-o-chlorodiphenylnitrilimine

The reaction period was increased to 7 days. Crystallization from methanol gave a mixture of regioisomers (**11d**, **12d**; 1.1 g, 39%) in a ratio of 3.5/1 (NMR). Exhaustive fractional crystallization from the same solvent allowed the isolation of samples of the 2 regioisomers. The major isomer (**11d**) was obtained as colorless granular crystals, m.p. 110–111.5°C: IR (KBr) 1714, 1590, 1478 cm^{-1}: ^1H NMR 2.48 (s, 3H, acetyl), 3.8



1a, R = $COCH_3$
b, R = CN
c, R = OCH_3

Figure 1

(br, 1H, 4-H) ppm: MS 340 (M^+, 5), 338 (M^+, 13), 297 (34), 295 (100), 259 (10), 111 (5), 77 (6), 43 (7) mu. Calculated for $C_{20}H_{19}N_2OCl$: C, 70.92; H, 5.65; N, 8.27; Cl, 10.47. Found: C, 70.69; H, 5.70; N, 8.13; Cl, 10.60. The minor isomer (**12d**) was obtained as colorless needles, m.p. 124–126°C: IR (KBr) 1710, 1588, 1480 cm^{-1}: ^1H NMR 2.28 (s, 3H, acetyl), 5.38 (t, br, 1H, 4-H): MS 340 (M^+, 18), 338 (M^+, 51), 297 (34), 268 (6), 259 (11), 130 (12), 111 (10), 77 (11), 43 (19) mu. Calculated for $C_{20}H_{19}N_2OCl$: C, 70.92; H, 5.65; N, 8.27; Cl, 10.47. Found: C, 70.65; H, 5.76; N, 8.16; Cl, 10.56.

Results and discussion

Compound **3b**[6] was accessible from 3β-hydroxyandrost-5-en-17-one (**2b**), which was converted to **3b** by treatment of its tosylhydrazone with methyl lithium (Scheme 1).[7] For the preparation of **5b** several routes were considered starting from 5α-androst-16-ene (**3a**).[8] The most direct route envisaged the treatment of **3a** with acetyl chloride in the presence of aluminum chloride, a method which had been used to produce 1-acetylcyclopentene from cyclopentene.[9] Steric effects were expected to favor 16-substitution. In practice the reaction led to a complex mixture, probably resulting from rearrangements of an intermediate 17-carbocation. The successful route to **5b** (Scheme 2) involved hydroboration/oxidation of **3a** with 9-borabicyclononane (9-BBN)[10] to yield 5α-androstan-16α-ol (**4a**) which was oxidized quantitatively to the ketone (**4b**)[5] by Jones' reagent. Successive treatment with HCN and $POCl_3$/pyridine gave the unsaturated nitrile (**5a**) by way of the epimeric cyanohydrins. Finally the 16-acetyl compound (**5b**) was produced by reaction of **5a** with methylmagnesium bromide.

Addition of diphenylnitrilimine to 3β-hydroxyandrost-5,16-diene (**3b**) gave, after acetylation, an inseparable 1/1 mixture (74%) of the two regioisomers (**6a**, **7a**) whose components could be readily identified by proton NMR (Table 1). The signals for the 16 and 17 protons were well separated and could be distinguished by their multiplicities. Comparison of the chemical shift values for the 16β-H in **6a** and **7a** clearly distinguished the [17α,16α-d] isomer (**7a**) as that with the more deshielded signal (4.72 δ) due to the attachment of the pyrazoline nitrogen to the 16-position.[2] Comparison of the 17β-H signals led to the same result with the 17β-H signal of **6a** occurring at the more deshielded value (4.28 δ). Additional proof of the assignments came from a comparison of the ^1H NMR spectrum of **7a** with that of a sample synthesized earlier[2] by an alternate route. Decoupling experiments confirmed the assignments.

To ascertain whether an ortho-substituent on the *C*-phenyl ring would bring about a change in the ratio of regioisomers due to a steric effect, *C*-*o*-chlorodiphenylnitrilimine was added to **3b** to give after acetylation a mixture of regioisomers, **6b**, **7b**, (87%) in the same 1/1 ratio indicating that a *C*-ortho substituent of this type exerts no directing effect. Again, the 16 and 17 proton signals could be readily distinguished (Table 1). The assignment of signals to the separate regioisomers was made easier in this case by the operation of the ortho-halogen effect[2] whereby the 16β or 17β protons adjacent to the *C*-phenyl rings were considerably deshielded.

In comparison with the additions described above, the addition of *N*-*o*-chlorodiphenylnitrilimine to **3b** was very slow with some starting material still present after 120 h at 70°C. In this case there was a marked regiochemical bias (5/1) in favor of the [17α,16α-d] isomer (**7c**), identified by its proton NMR data, in particular the very low field signal of the 16β-H at 5.33 ppm due to the ortho-halogen effect. The minor isomer (**6c**) showed the expected ortho-halogen downfield shift (0.46 ppm) of its 17β-H.

The 16,17-androstene (**3b**) was chosen as a substrate for this study because the double bond is almost symmetrically substituted. The difference in electronic effect of a quaternary alkyl site at C-13 and a secondary alkyl site at C-15 on the electronic distribution in the 16,17 double bond should be extremely small leading to essentially equal coefficient magnitudes at C-16 and C-17 in both the HOMO and LUMO of this dipolarophilic site. Consequently frontier orbital considerations[11,12] should not apply in this situation and differences in proportions of regioisomers can therefore be attributed solely to steric effects. This argument is borne out by the generation of equal amounts of regioisomers in the pairs **6a**, **7a** and **6b**, **7b**. The 5/1 ratio of regioisomers **7c**, **6c** indicates a considerable steric effect for ortho substitu-

Table 1 Proton NMR data for steroidal diphenylpyrazolines

Compound	16β-H	17β-H
6a	4.16 dt	4.28 d (9.9)
6b	4.55[a] m	4.28 d (10.2)
6c	4.34 m	4.74[a] d (8.1)
7a	4.72 dd (10.5, 5.6)	3.90 d (10.5)
7b	4.77 dd (10.7, 5.9)	4.44[a] d (10.7)
7c	5.33[a] dd (10.2, 5.6)	3.86 d (10.2)
8a		3.74 s
8b		4.39 s
9a		4.25 s
9b		4.41 s

Chemical shift values are given in ppm downfield from TMS. Letters following chemical shift values refer to multiplicity and numbers in parentheses are coupling constants in Hz.
[a] Ortho-halogen effect (0.4–0.6 ppm downfield shift)

tion of the *N*-phenyl ring in the dipole. This would be in accord with an endo approach of the dipole (central nitrogen directed inward) using the dipole geometry proposed by Huisgen.[13] This leads to steric interaction between the *N*-phenyl ring and the C-11, C-12 underside of the steroid.

As a consequence of the results described above and the earlier work on additions to steroidal 17-acyl-16-enes,[2] it became of interest to study additions to 16-acetyl-16-enes in the expectation that predominant electronic control would lead to exclusive formation of the 17α,16α-d regioisomers. Addition of diphenylnitrilimine to 16-acetyl-5α-androst-16-ene (**5b**) gave a 74% yield of a 6/1 mixture of regioisomers. The major isomer was the predicted [17α,16α-d] compound (**8a**) which showed a singlet for the 17β-H at 3.74 ppm. In the minor isomer (**9a**) the corresponding singlet fell at lower field (4.30 ppm) as expected. The reason for the formation of a small amount of the [16α,17α-d] regioisomer in contrast to the results from the 17-acetyl-16-enes is not clear. In the addition of *C*-*o*-bromodiphenylnitrilimine to **5b** the same 6/1 ratio of regioisomers was observed (85% yield) with the [17α,16α-d] isomer (**8b**) predominating. The 17β-H signal of the major isomer (**8b**) appeared at the downshifted value of 4.39 ppm as a result of the ortho-halogen effect. Although this value is almost identical with that of the minor isomer (**9b**) at 4.41 ppm, the major isomer was identified by its TLC polarity and by the presence of a distinctive triplet ($J = 14$ Hz) at 2.5 ppm attributed to the 15β-H which must fall in the deshielding cone of the ketone carbonyl group. This signal is also present in the corresponding regioisomer (**8a**) in the phenyl-unsubstituted series.

In order to determine if the steroid skeleton was having an influence on the regiochemical outcome, it was decided to study additions to the simple analog, 1-acetylcyclopentene (**10**). Treatment with diphenylnitrilimine gave as the predominant product the [2,1-d] regioisomer (**11a**) whose identity was determined by the chemical shift value (4.02 ppm) of the H-2 multiplet. A trace of the [1,2-d] isomer (**12a**) was detected by NMR analysis of the mother liquors. An exactly comparable result was obtained in the addition of *C*-*p*-chlorodiphenylnitrilimine to 1-acetylcyclopentene (**10**) yielding **11b** (major) and **12b** (trace). In the addition of *C*-*o*-chlorodiphenyldiphenylnitrilimine the [2,1-d] regioisomer (**11c**) was the exclusive product. It displayed the expected ortho-halogen downfield shift of H-2 (4.49 ppm). These results are essentially comparable to those in the steroid field. In contrast, *N*-*o*-chlorodiphenylnitrilimine combined with 1-acetylcyclopentene (**10**) to give a regioisomer ratio of 3.5/1 in favor of the [2,1-d] adduct (**11d**) which showed an H-2 signal at 3.80 ppm. The minor [1,2-d] isomer (**12d**) displayed the expected strongly deshielded signal for H-2 at 5.38 ppm. As in the case of the steroid reactions, the addition of the *N*-*ortho*-substituted nitrilimine was much slower than other additions and resulted in lower yield.

In all reactions studied so far involving the addition of diphenylnitrilimines to steroidal and monocyclic acylcyclopentenes, the major, and in some cases the exclusive, product is that in which the nitrogen atom bonds to the carbon carrying the acyl group (5-acylpyrazolines). Halogen substituents at the ortho position on the *C*-phenyl ring of the dipole exert at best a very minor effect, whereas halogens on the *N*-phenyl ring have a measurable effect on the ratio of regioisomers in the cyclopentene series, leading to an increase in proportion of the minor regioisomer.

Although the regiochemical outcome in 1,3-dipolar additions to electronically biassed dipolarophiles is undoubtedly controlled by frontier orbital interactions, the reason for the predominant formation of 5-acylpyrazolines in the addition of diphenylnitrilimine to α,β-unsaturated ketones is still not clear. Houk[12] et al. have predicted that the dominant interaction should be HOMO-dipole/LUMO-dipolarophile but this would lead to 4-acylpyrazolines based on his calculated orbital coefficients[11] for the dipole. Gandolfi[14] and co-workers have rationalized the results by suggesting that the dipole coefficient magnitudes may in fact be reversed with the *C* coefficient slightly larger than the terminal *N* coefficient. Although he advanced no new calculations to support this possibility, he did cite Bastide and Henri-Rousseau,[15] whose calculations, including resonance integrals, indicated the carbon atom of the dipole to be the more nucleophilic site. On the other hand, the predominant formation of 5-acylpyrazolines might also be explained in terms of a dominance of the LUMO-dipole/HOMO-dipolarophile interaction. In view of the uncertainties in this area, it seems futile to attempt to explain small changes in regioisomer ratios in these terms.

In the absence of substitution of the double bond by strongly interacting groups such as acetyl, steric effects should dominate as demonstrated by the considerable effect on product ratio of *N*-*o*-halogen substitution in addition to compound **3b**. Efforts are continuing to delineate the directing factors involved in this useful synthesis of steroidal fused-ring pyrazolines.

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