Regioselective reactions of 1,2-dehydroprogesterone: syntheses of pregnane derivatives as possible contragestational agents

Dibyendu De, Manju Seth, and Amiya Prasad Bhaduri

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow, India

A few pregnane derivatives were synthesized from 1,2-dehydroprogesterone ***(1)****. Ring A of 1,2-dehydroprogesterone was aromatized without affecting C-20, and the resulting acetoxy compound* ***(2)*** *after hydrolysis yielded 1-hydroxy-4-methyl-19-norpregna-1,3,5(10)-trien-20-one* ***(3)****. Reactions of the phenol* ***(3)*** *with alkyl halides yielded the ethers* ***6a-6b*** *and* ***7****. Opening of the oxirane ring in* ***7*** *with secondary amines furnished the aminoalcohols* ***8a-8b****. Friedelcraft's reaction of* ***3*** *with maleic anhydride and chloracetyl chloride led to the formation of* ***9*** *and* ***10****, respectively. Base-catalyzed ring closure of* ***10*** *yielded 1-acetyl-12a-methyl-8-oxo-5[H]-1,2,3,3a,3b,4,8,9,10b,11,12,12a-dodecahydrocyclopenta* ***(7,8)****-phenanthro* ***(3,4-b)*** *furan* ***(11)****, which reacted with aromatic aldehydes regioselectively to furnish* ***12a-12b****. Reaction of* ***1*** *with triethylorthoformate in the presence of boron trifluoride etherate involved the participation of C-21, and the carbonyl at C-3 remained unaffected. The product* ***13*** *was identified as 21-[2-hydroxyvinyl]-21-norpregna-1,4-diene-3,20-dione. Reductive amination with sodium cyanoborohydride in the presence of ammonium acetate did not attack ring A and smoothly furnished the amine* ***14*** *which, on reaction with succinic anhydride, gave 20-succinamylpregna-1,4-dien-3-one* ***(15)****. (Steroids* **56:**189–194, 1991)

Keywords: steroids; 1,2-dehydroprogesterone; aromatization; Friedelcraft's acylation; regioselective reaction

Introduction

Steroids that antagonize the action of progesterone are under clinical evaluation.[1] However, steroids lacking hormonal properties may also interfere with the uteroplacental complex to prevent pregnancy. This possibility appears to be unexplored. The present work describes syntheses of pregnane derivatives from 1,2-dehydroprogesterone, modifications at C-3 and/or at C-17 or C-20 of the pregnane derivative, which may lead to loss of frank hormonal property[2] without affecting its envisaged action on uteroplacental junction. The design of pregnane derivatives reported here is based on this concept. Syntheses of the title compounds are presented; their profile of hormonal and antifertility activities will be published elsewhere.

Address reprint requests to Dr. Amiya Prasad Bhaduri, Medicinal Chemistry Division, Central Drug Research Institute, Chattar Manzil, Post Box No. 173, Lucknow—226 001, India.
Received August 22, 1990; accepted October 5, 1990.

Experimental

Except when otherwise mentioned, a standard procedure was used for product isolation. This procedure involved quenching by addition of water, exhaustive extraction with an organic solvent, washing the extracts with water, drying with sodium sulfate, filtration, and evaporation of the solvent under reduced pressure. The particular solvents and aqueous washes used are mentioned in parentheses after the phrase "product isolation."

Thin-layer chromatography (TLC) was performed using 0.25-mm silica gel glass-backed plates. Visualization was accomplished by UV light, iodine vapor, or potassium permanganate solution. "Room temperature" indicates a temperature between 25 and 30 C.

Melting points (mp) were determined on a precision electronic melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Perkin-Elmer model 157 or Beckman Acculab-1 spectrophotometers. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained on a Perkin-Elmer R-32 (90 MHz) or Bruker WM-400 FT (400 MHz) spectrometer using tetrameth-

ylsilane as an internal standard. The data are reported in the form δ value of signal (Peak multiplicity, coupling constant [if applicable] in Hz, number of protons, assignment). The mass spectra were recorded on a JEOL-JMS-D-300 mass spectrometer.

1-Acetyloxy-4-methyl-19-norpregna-1,3,5(10)-trien-20-one **(2)**

1,2-Dehydroprogesterone (**1**; 10 g, 32 mmol) was added slowly to an ice-cold mixture of acetic anhydride (22 ml, 230 mmol) and boron trifluoride etherate (22 ml, 170 mmol). The resulting mixture was stirred at room temperature for 6 hours and, after completion of the reaction (TLC, silica gel, $CHCl_3$), was poured on finely crushed ice (400 g) with stirring and was left at 10 C for 24 hours. The separated solid product was filtered, washed with water, dried in vacuo, and recrystallized from ethanol (10.2 g, 90%); mp, 136 to 137 C; IR (KBr) 1,730, 1,685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (S, 3H, 18-CH_3), 2.04 (S, 3H, 4-CH_3), 2.10 (S, 3H, 21-CH_3), 2.19 (S, 3H, $OCOCH_3$), 6.60 (d, J = 8, 1H, 3-H), 6.84 (d, J = 8, 1H, 2H); mass spectrum, m/z 354 (M^+) 339, 312. Analysis calculated for $C_{23}H_{30}O_3$: C, 77.96; H, 8.47. Found: C, 77.76; H, 8.58.

1-Hydroxy-4-methyl-19-norpregna-1,3,5(10)-trien-20-one **(3)**

A solution of compound **2** (10 g, 28 mmol) in 2% methanolic KOH solution (30 ml) was stirred at 25 C for 5 hours. Excess MeOH was evaporated under reduced pressure and the residue neutralized with cold 5% AcOH solution. The separated solid product was filtered, washed with water, and recrystallized from EtOH (6.65 g, 75%): mp, 211 to 212 C; IR (KBr) 3,420, 1,680 cm^{-1}; ^1H NMR ($CDCl_3$) 0.60 (s, 3H, 18-CH_3), 2.06 (s, 3H, 4-CH_3), 2.08 (s, 3H, 21-CH_3), 6.45 (d, J = 8, 1H, 3-H), 6.68 (d, J = 8, 1H, 2-H), 8.28 (s, 1H, OH); mass spectrum, m/z 312 (M^+), 227. Analysis calculated for $C_{21}H_{27}O_2$: C, 80.76; H, 8.65. Found: C, 80.87, H, 8.79.

3-Chloropregna-1,3,5(6)-trien-20-one **(4)**

Dry *N,N*-dimethyl formamide (DMF) (1.4 ml, 18 mmol) was added to ice-cold phosphorous oxychloride (1.6 ml, 17 mmol). The resulting solution was stirred at 10 C for 30 minutes. It was then cooled to 0 C and to this solution was added **1** (1 g, 3 mmol) in dry DMF (1.8 ml). The reaction was allowed to continue at 5 to 10 C for 2 hours; thereafter, crushed ice was poured into the reaction mixture which was left overnight at 5 C. The separated solid product was filtered, washed with water, and dried in vacuo. The product thus obtained was recrystallized from EtOH (1 g, 95%): mp, 105 to 106 C; IR (KBr) 1,700 cm^{-1}; ^1H NMR ($CDCl_3$) 0.75 (s, 3H, 18-CH_3), 1.04 (s, 3H, 19-CH_3), 2.08 (s, 3H, 21-CH_3), 5.45 (m, 1H, 6-H), 5.78 (d, J = 8, 1H, 1-H), 5.89 (dd, J = 1, 8, 1H, 2-H), 5.91 (d, J = 1, 1H, 4-H); mass spectrum, m/z 330 (M^+), 332, 152, 154. Analysis calculated for $C_{21}H_{27}ClO$: C, 76.36; H, 8.18. Found: C, 76.49; H, 8.28.

1-Chloro-4-methyl-19-norpregna-1,3,5(10)-trien-20-one **(5)**

To a solution of compound **4** (0.9 g, 3 mmol) in dichloromethane (10 ml) was added boron trifluoride etherate (0.8 ml, 6 mmol), and the mixture was stirred at room temperature for 2 days. Excess solvent was evaporated under reduced pressure and acetone (8 ml) was added to the residue. The resulting mixture was allowed to stand at 10 C for 24 hours. The crude thus isolated was recrystallized from EtOH (0.45 g, 50%): mp, 189 to 190 C (lit. mp[2], 192 C); IR (KBr) 1,675 cm^{-1}; ^1H NMR ($CDCl_3$) 0.64 (s, 3H, 18-CH_3), 2.08 (s, 3H, 4-CH_3), 2.12 (s, 3H, 21-CH_3), 6.77 (d, J = 8, 1H, 3-H), 6.98 (d, J = 8, 1H, 2-H); mass spectrum, m/z 330 (M^+), 332. Analysis calculated for $C_{21}H_{27}ClO$: C, 76.36; H, 8.18. Found: C, 76.40; H, 8.08.

1-(2-N,N-Diethylaminoethoxy)-4-methyl-19-norpregna-1,3,5(10)-trien-20-one **(6a)**

Compound **3** (0.5 g, 1.6 mmol) was added to a suspension of sodium hydride (50%; 0.65 g, 13 mmol, washed with dry benzene) in DMF (1.2 ml) under stirring. To this mixture was then added *N,N*-diethylamino ethylamine (0.6 g), and the reaction mixture was stirred at room temperature for 6 hours. Product isolation ($CHCl_3$, water, brine) and purification (basic alumina, $C_6H_6/CHCl_3$, 1 : 1) furnished pure oil product (0.5 g, 75%): IR (neat) 1,710 cm^{-1}; ^1H NMR ($CDCl_3$) 0.61 (s, 3H, 18-CH_3), 0.98 (m, 6H, CH_2CH_3), 2.06 (s, 6H, 4-CH_3, 21-CH_3), 2.55 (m, 6H, N-CH_2), 3.86 (t, J = 6, 2H, OCH_2), 6.45 (d, J = 8, 1H, 3-H), 6.75 (d, J = 8, 1H, 2-H); mass spectrum, m/z 441 (M^+), 396. Analysis calculated for $C_{28}H_{43}NO_3$: C, 76.19; H, 9.75; N, 3.17. Found: C, 75.95; H, 9.62; N, 3.30.

4-Methyl-1-(2-pyrrolidinoethoxy)-19-norpregna-1,3,5(10)-trien-20-one **(6b)**

Following the methods described for the preparation and purification of compound **6a**, compound **6b** was obtained as an oil (70%): IR (neat) 1,695 cm^{-1}; ^1H NMR ($CDCl_3$) 0.56 (s, 3H, 18-CH_3), 0.82 (m, 4H, CH_2-C), 1.95 (s, 3H, 4-CH_3), 2.0 (s, 3H, 21-CH_3), 2.48 (m, 4H, N-CH_2), 2.72 (m, 2H, NCH_2), 6.65 (d, J = 8, 1H, 2-H); mass spectrum, m/z 409 (M^+), 338. Analysis calculated for $C_{27}H_{39}NO_2$: C, 79.21; H, 9.53; N, 3.42. Found: C, 79.05; H, 9.64; N, 3.56.

4-Methyl-1-[(2,3-epoxy)propoxy]-19-norpregna-1,3,5(10)-trien-20-one **(7)**

Potassium hydroxide (0.8 g, 14 mmol) was added to a solution of compound **3** (1 g, 3 mmol) in dimethyl sulfoxide (2 ml), and the resulting mixture was stirred for 15 minutes at room temperature. 1-Chloro-2,3-epoxypropane (0.8 ml, 10 mmol) was then added to this mixture, and the reaction was allowed to continue at 80 C for 7 hours. The reaction mixture was finally cooled to room temperature and then quenched with water (80 ml). Product isolation ($CHCl_3$, brine, water) and purification (florisil, benzene/$CHCl_3$, 1 : 5 v/v) furnished oil

compound (0.9 g, 80%): IR (neat) 1,708 cm^{-1}; ^1H NMR ($CDCl_3$) 0.58 (s, 3H, 18-CH_3), 2.0 (s, 3H, 4-CH_3), 2.06 (s, 3H, 21-CH_3), 3.48 (m, 1H, OCH), 3.90 (m, 4H, OCH_2), 6.38 (d, J = 8, 1H, 3-H), 6.68 (d, J = 8, 1H, 2-H); mass spectrum, m/z 368 (M^+). Analysis calculated for $C_{24}H_{32}O_3$: C, 78.26; H, 8.63. Found: C, 78.06; H, 8.83.

1-[(3-N,N-Diethylamino-2-hydroxy)propoxy]-4-methyl-19-norpregna-1,3,5(10)-trien-20-one ***(8a)***

Compound **7** (0.5 g, 1.3 mmol) was dissolved in MeOH (4 ml), and diethylamine (1.6 ml, 15 mmol) was added to the mixture, which was then refluxed for 5 hours. Excess MeOH was evaporated under reduced pressure, and water (50 ml) was added to the residue. Product isolation ($CHCl_3$, brine, water) and purification (basic alumina, $C_6H_6/CHCl_3$, 3 : 1 v/v) furnished the product as oil (0.45 g, 75%): IR (neat) 3,400, 1,690 cm^{-1}; ^1H NMR (CCl_4) 0.60 (s, 3H, 18-CH_3), 0.98 (m, 6H, CH_2CH_3), 1.95 (s, 3H, 4-CH_3), 2.04 (s, 3H, 21-CH_3), 2.48 (m, 6H, NCH_2), 2.98 (m, 1H, CH-O), 3.75 (m, 2H, CH_2-O), 6.35 (d, J = 8, 1H, 3-H), 6.63 (d, J = 8, 1H, 2-H); mass spectrum, m/z 441 (M^+), 312. Analysis calculated for $C_{28}H_{43}NO_3$: C, 76.19; H, 9.75; N, 3.17. Found: C, 76.31, H, 9.65; N, 3.25.

1-[3-N,N-Diisopropylamino-2-hydroxy]propoxy-4-methyl-19-norpregna-1,3,5(10)-trien-20-one ***(8b)***

Following the method described for the preparation and purification of compound **8a**, compound **8b** was obtained as an oil (75%): IR (neat) 3,405, 1,690 cm^{-1}; ^1H NMR ($CDCl_3$) 0.60 (s, 3H, 18-CH_3), 1.03 (m, 12H, $CHCH_3$), 2.01 (s, 3H, 4-CH_3), 2.08 (s, 3H, 21-CH_3), 2.58 (m, 2H, NCH_2), 3.05 (m, 2H, NCH_2), 3.64 (m, 1H, CH), 3.90 (m, 2H, CH_2-O), 6.53 (d, J = 8, 1H, 3-H), 6.83 (d, J = 8, 1H, 2-H); mass spectrum, 441 (M^+). Analysis calculated for $C_{30}H_{47}NO_3$: C, 76.75; H, 10.02; N, 2.98. Found: C, 76.65; H, 9.89; N, 3.10.

2-[3-Carboxy-1-oxo-2-propenyl]-1-hydroxy-19-norpregna-1,3,5(10)-trien-20-one ***(9)***

Maleic anhydride (1.1 g, 11 mmol) was dissolved in dry dichloromethane (10 ml), and anhydrous aluminum chloride (1.6 g, 12 mmol) was added to the solution. The resulting mixture was cooled to 5 C, then compound **3** (0.7 g, 2.2 mmol) was added with stirring. The resulting reaction mixture was stirred at room temperature for 2 hours; thereafter, ice (50 g) was added slowly to quench the reaction. To this mixture was added 30% HCl solution (50 ml). Product isolation ($CHCl_3$, water, brine) furnished crude product that, without further purification, was subjected to appropriate reactions.

2-[3-Carbomethoxy-1-oxo-2-propenyl]-1-hydroxy-19-norpregna-1,3,5(10)-trien-20-one ***(9a)***

To an ice-cold solution of crude compound **9** (1.2 g) in dry MeOH (2 ml) was added sulfuric acid (d 1.80, 0.3 ml); the mixture was stirred at room temperature for 5 hours. After completion (TLC, silica gel, $CHCl_3$/EtOAC, 5 : 1 v/v), the mixture was diluted with water (80 ml). Product isolation ($CHCl_3$, $NaHCO_3$, brine, water) and purification (silica gel, EtOAC/hexane, 1 : 5 v/v) furnished pure oil product (0.9 g, 70%): IR (neat) 1,730, 1,695, 1,620 cm^{-1}; ^1H NMR ($CDCl_3$) 0.68 (s, 3H, 18-CH_3), 2.08 (s, 3H, 4-CH_3), 2.16 (s, 3H, 21-CH_3), 3.80 (s, 3H, $COOCH_3$), 6.84 (d, J = 14, 1H=CH), 7.31 (s, 1H, 3-H), 7.91 (d, J = 14, 1H=CH); mass spectrum, 434 (M^+). Analysis calculated for $C_{26}H_{32}O_5$: C, 73.58; H, 7.54. Found: C, 73.42; H, 7.65.

2-[3-Carbomethoxy-2-methoxy-1-oxo-prop-1-yl]-1-hydroxy-4-methyl-19-norpregna-1,3,5(10)-trien-20-one ***(9b)***

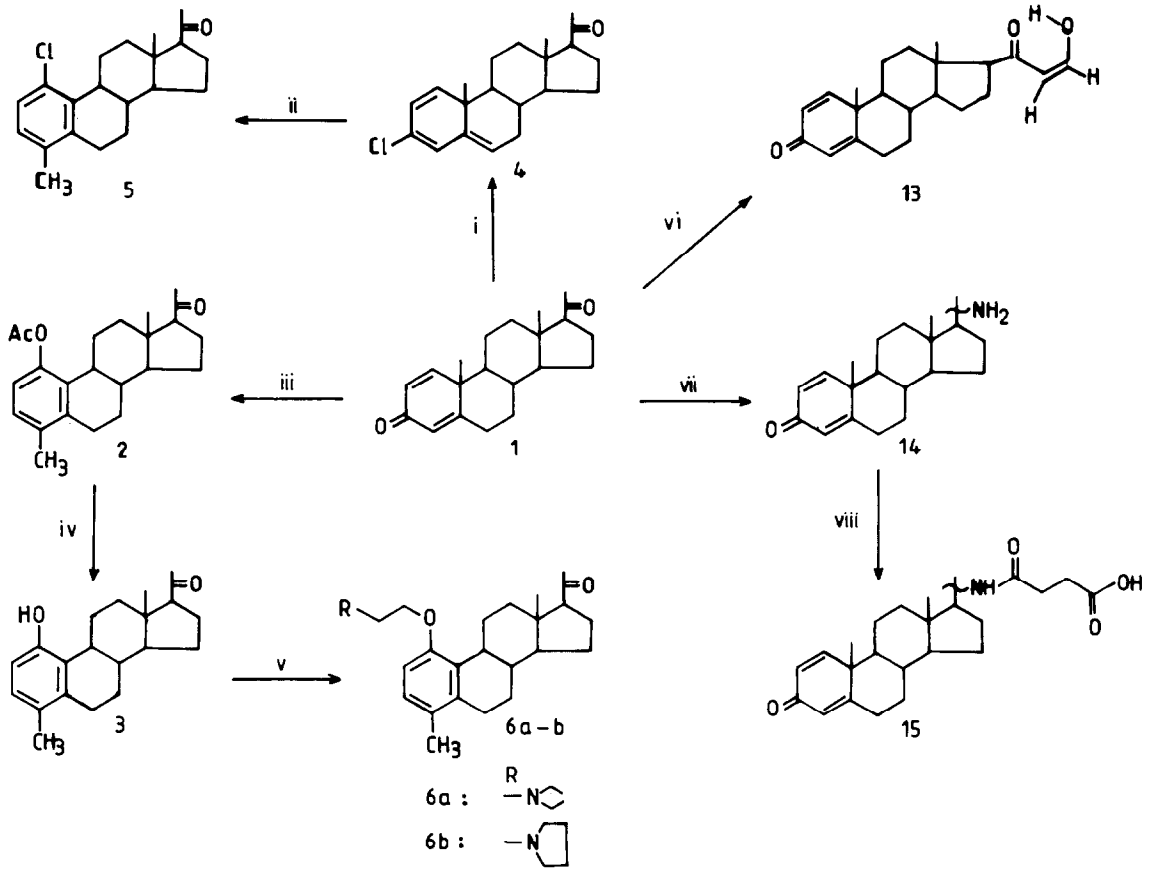
To a solution of compound **9** (0.7 g) in dry MeOH (4 ml) was added boron trifluoride etherate (0.3 ml), and the mixture was stirred for 3 hours at room temperature. Excess MeOH was evaporated and reaction was quenched with ice (30 g). Product isolation ($CHCl_3$, $NaHCO_3$, brine, water) followed by filtration through Florisil (benzene/hexane, 1 : 1 v/v) furnished pure compound as oil (0.6 g, 75%): IR (neat) 1,760, 1,708, 1,620 cm^{-1}; ^1H NMR ($CDCl_3$) 0.60 (s, 3H, 18-CH_3), 2.0 (s, 3H, 4-CH_3), 2.08 (s, 3H, 21-CH_3), 2.50 (m, 2H, CH_2-CO), 3.32 (s, 3H, OCH_3), 3.65 (s, 3H, $COOCH_3$), 4.21 (t, J = 5, 1H, CH-O), 7.18 (s, 1H, 3-H); mass spectrum, m/z 456 (M^+), 365. Analysis calculated for $C_{27}H_{36}O_6$: C, 71.05; H, 7.89. Found: C, 70.88; H, 7.95.

2-[2-Chloro-1-oxoethyl]-1-hydroxy-4-methyl-19-norpregna-1,3,5(10)-trien-20-one ***(10)***

To an ice-cold solution of compound **3** (2 g, 6.4 mmol) in dry dichloromethane were added chloracetyl chloride (1.4 ml, 17.3 mmol) and anhydrous aluminum chloride (1.6 g, 12 mmol) with stirring. The resulting reaction mixture was stirred at room temperature for 2 hours; thereafter, ice (100 g) was added slowly to quench the reaction. To this mixture was added 30% HCl solution (50 ml). Product isolation ($CHCl_3$, water, brine) and trituration in hexane gave a solid product that was recrystallized from chloroform (2.2 g, 90%): mp, 155 to 156 C; IR (KBr) 1,620, 1,700 cm^{-1}; ^1H NMR ($CDCl_3$) 0.70 (s, 3H, 18-CH_3), 2.07 (s, 3H, 4-CH_3), 2.11 (s, 3H, 21-CH_3), 4.60 (s, 2H, CH_2-CO), 7.20 (s, 1H, 3H); mass spectrum, m/z 388 (M^+), 390 (M + 2). Analysis calculated for $C_{23}H_{29}ClO_3$: C, 71.13; H, 7.47. Found: C, 71.26; H, 7.65.

1-Acetyl-12a-methyl-8-oxo-5[H]-1,2,3,3a,3b,4,8,9,10b,11,12,12a-dodecahydrocyclopenta[7,8]phenanthro[3,4-b]furan ***(11)***

To the suspension of compound **10** (1.6 g, 4.3 mmol) in MeOH (10 ml) was added adhydrous sodium acetate (0.8 g, 9.7 mmol) with stirring. The mixture was allowed to reflux for 5 hours. Excess MeOH was evaporated and reaction was quenched with ice water. The separated solid compound was filtered and washed with



Scheme 1 i, $POCl_3$/DMF; ii, $BF_3 \cdot Et_2O$; iii, $Ac_2O/BF_3 \cdot Et_2O$; iv, KOH/MeOH; v, RCl/NaH/DMF; vi, $BF_3 \cdot Et_2O/HC(OEt)_3$; vii, NH_4OAc/$NaBH_3CN$/THF/MeOH; viii, succinic anhydride/THF.

water and dried. The product was recrystallized from $CHCl_3$ (1.2 g, 80%): mp, 147 to 148 C; IR (KBr) 1,605, 1,700 cm^{-1}; ^1H NMR ($CDCl_3$) 0.67 (s, 3H, 18-CH_3), 2.05 (s, 3H, 4-CH_3), 2.10 (s, 3H, 21-CH_3), 4.45 (s, 2H, CH_2-CO), 7.16 (s, 1H, 3-H); mass spectrum, m/z, 352 (M^+), 312. Analysis calculated for $C_{23}H_{28}O_3$: C, 78.40; H, 7.95. Found: C, 78.25; H, 7.85.

E-1-Acetyl-9-[4-hydroxyphenylmethylene]-12a-methyl-8-oxo-5[H]-1,2,3,3a,3b,4,8,9,10b,11,12,12a-dodecahydrocyclopenta[7,8]phenanthro[3,4-b]furan (12a)

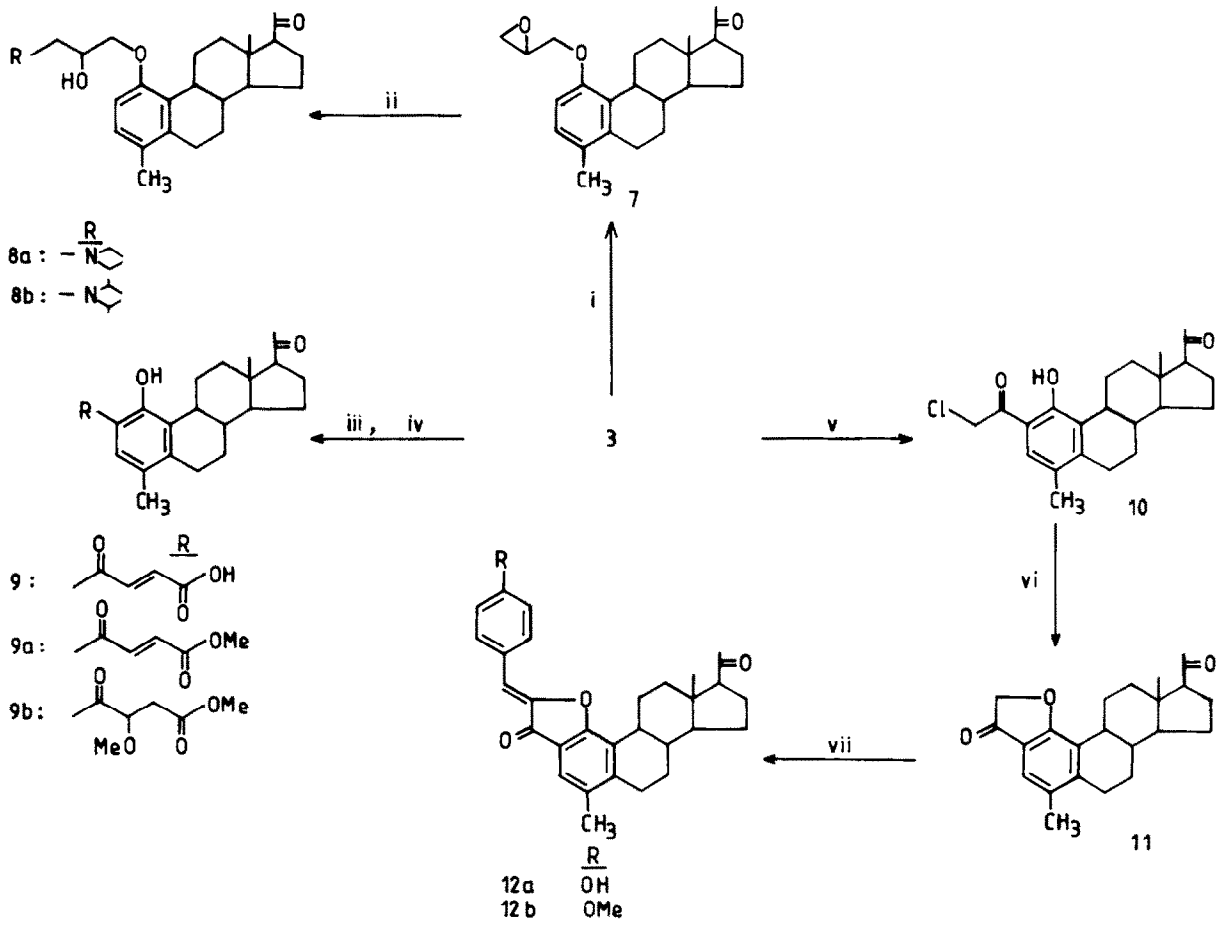
To a solution of compound **11** (0.6 g, 1.8 mmol) in tetrahydrofuran (15 ml) were added p-hydroxybenzaldehyde (0.22 g, 1.8 mmol) and piperidine (0.6 ml, 6.8 mmol). The mixture was heated to reflux at 80 C with stirring for 7 hours. Excess solvent was evaporated under reduced pressure and hexane (20 ml) was added to the residue. The crude product was recrystallized from $CHCl_3$ (0.72 g, 90%): mp, 235 to 236 C; IR (KBr) 1,600, 1,695 cm^{-1}; ^1H NMR ($CDCl_3$) 0.65 (s, 3H, 18-CH_3), 2.08 (s, 3H, 4-CH_3), 2.15 (s, 3H, 21-CH_3), 6.65 (s, 1H, CH), 6.82 (d, J = 8, 2H, Ar-H), 7.23 (s, 1H, 3-H), 7.65 (d, J = 8, 2H, Ar-H); mass spectrum, m/z 456 (M^+). Analysis calculated for $C_{30}H_{32}O_4$: C, 78.94; H, 7.01. Found: C, 79.11; H, 7.25.

E-1-Acetyl-9-[4-methoxyphenylmethylene]-12a-methyl-8-oxo-5[H]-1,2,3,3a,3b,4,8,9,10b,11,12,12a-dodecahydrocyclopenta[7,8]phenanthro[3,4-b]furan (12b)

Melting point, 194 to 195 C; IR (KBr) 1,600, 1,700 cm^{-1}; ^1H NMR ($CDCl_3$) 0.70 (s, 3H, 18-CH_3), 2.12 (s, 3H, 4-CH_3), 2.17 (s, 3H, 21-CH_3); 3.82 (s, 3H, OCH_3), 6.71 (s, 1H, CH), 6.88 (d, J = 8, 2H, Ar-H), 7.31 (s, 1H, 3-H), 7.75 (d, J = 8, 2H, Ar-H); mass spectrum, m/z 470 (M^+), 352. Analysis calculated for $C_{31}H_{34}O_4$: C, 79.14; H, 7.23. Found: C, 79.23; H, 7.35.

21-[2-Hydroxyvinyl]-21-norpregna-1,4-diene-3,20-dione (13)

Triethylorthoformate (2.5 ml, 14.5 mmol) was added to boron trifluoride etherate (3.2 ml, 25 mmol) at 0 C, and the resulting mixture was stirred for 10 minutes. Compound **1** (1 g, 3 mmol) was added to this solution, and the reaction mixture was stirred at 10 C for 2 hours. After completion (TLC, benzene/$CHCl_3$ 1 : 1), the reaction was quenched by crushed ice (20 g). Product isolation ($CHCl_3$, brine) gave the pure product as oil (0.87 g, 80%): IR (neat) 3,415, 1,650, 1,610 cm^{-1}; ^1H NMR ($CDCl_3$) 0.68 (s, 3H, 18-CH_3), 1.18 (s, 3H, 19-CH_3), 5.35 (d, J = 6, 1H, 21-H), 5.92 (s, 1H, 4-H), 6.08 (dd,



Scheme 2 i, 1,2-epichlorhydrin/KOH/DMSO; ii, RRNH/MeOH; iii, maleic anhydride/Al_2O_3/CH_2Cl_2; iv, H_2SO_4/MeOH or BF_3 Et_2O/MeOH; v, $ClCOCH_2Cl/AlCl_3/CH_2Cl_2$; vi, NaOAc; vii, ArCHO/piperidine.

J = 2, 10, 1H, 2-H), 6.90 (d, J = 10, 1H, 1-H), 7.78 (d, J = 6, 1H, 22-H); mass spectrum, m/z 340 (M^+), 322, 312. Analysis calculated for $C_{22}H_{28}O_3$: C, 77.64; H, 8.23. Found: C, 77.45; H, 8.51.

20-Aminopregna-1,4-dien-3-one (**14**)

Compound **1** (1 g, 3 mmol) was dissolved in a mixture of dry MeOH (10 ml) and dry tetrahydrofuran (20 ml). Ammonium acetate (2.7 g, 35 mmol) was added to this solution, and the resulting mixture was stirred at room temperature for 30 minutes. Sodium cyanoborohydride (0.35 g) was then added slowly to this mixture, and the reaction was allowed to continue at room temperature for 4 days. The precipitated solid was filtered, and the filtrate was poured into ice-cold NH_4OH (1N, 80 ml). Product isolation ($CHCl_3$, water, brine) furnished isomeric mixture of amine[3] as oil in quantitative yield: IR (neat) 2,920, 1,650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 0.74 (s, 3H, 18-CH_3), 1.04 (d, J = 7, 3H, 21-CH_3), 1.11 (d, J = 7, 3H, 21-CH_3), 1.22 (s, 3H, 19-CH_3), 1.24 (s, 3H, 19-CH_3), 2.85 (m, 2H, 2 × 20-H), 6.07 (s, 1H, 4-H), 6.08 (s, 1H, 4-H), 6.24 (dd, J = 2, 10, 1H, 2-H), 6.25 (dd, J = 2, 10, 1H, 2-H), 7.07 (d, J = 10, 1H, 1-H), 7.08 (d, J = 10, 1H, 1-H); mass spectrum, m/z 313 (M^+), 298. Analysis calculated for $C_{21}H_{31}NO$: C, 80.51; H, 9.90; N, 4.48. Found: C, 80.39; H, 9.36; N, 4.52.

20-Succinamylpregna-1,4-dien-3-one (**15**)

Succinic anhydride (0.2 g, 2 mmol) was added to the solution of compound **8** (0.5 g, 1.6 mmol) in dry benzene (8 ml). It was stirred at room temperature for 10 hours. After completion (TLC silica gel, 5% MeOH/$CHCl_3$), water (80 ml) was added to it. Product isolation ($CHCl_3$, brine, water) followed by recrystallization from $CHCl_3$/hexane furnished the desired product as a mixture of isomers (0.45 g, 68%): mp, 146 to 148 C (decomposition); IR (KBr) 1,720, 1,650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 0.76 (s, 3H, 18-CH_3), 0.86 (s, 3H, 18-CH_3), 1.10 (d, J = 7, 3H, 21-CH_3), 1.18 (d, J = 7, 3H, 21-CH_3), 1.24 (s, 3H, 19-CH_3), 1.25 (s, 3H, 19-CH_3), 2.47 (t, J = 7, 4H, CH_2-CO), 4.01 (m, 2H, 20-H), 6.08 (s, 1H, 4-H), 6.24 (dd, J = 2, 10, 1H, 2-H), 6.25 (dd, J = 2, 10, 1H, 2-H), 7.06 (d, J = 10, 1H, 1-H), 7.07 (d, J = 10, 1H, 1-H); mass spectrum, m/z 413 (M^+), 395. Analysis calculated for $C_{25}H_{35}NO_4$: C, 69.60; H, 8.10; N, 3.20. Found: C, 69.80; H, 8.21; N, 3.08.

Results and discussion

Two strategies were used for the synthesis of pregnane derivatives. The first was concerned with the changes made only in ring A of 1,2-dehydroprogesterone **(1)** and the second related to the changes made exclusively at position 20 of compound **1**. Aromatization of ring A in **1** was carried out by earlier investigators,[2,4,5] and one of the most common methods used earlier related to the use of acetic anhydride and *p*-toluenesulfonic acid mixture. This method invariably led to the formation of 1,20-diacetoxy-4-methyl-19-norpregna-1,3,5(10),17(20)-tetraene.[4]

In the present study, it has been observed that the reaction of **1** with acetic anhydride in the presence of boron trifluoride etherate exclusively furnished **2** (Scheme 1) and C-20 was not involved in the reaction. Reaction of **1** with oxalyl chloride, reported earlier,[2] led to the formation of **5**. However, no intermediate could be trapped in this reaction. In the present study, Vilsmeier-Haack reaction of **1** with phosphorous oxychloride and *N*,*N*-dimethyl formamide gave the desired intermediate **4** in quantitative yield, and its reaction with boron trifluoride etherate in dichloromethane furnished **5** in good yield. Alkaline hydrolysis of compound **2** furnished **3**. Base-catalyzed reaction of **3** with appropriate halides gave the ethers **6a-6b** and **7** (Schemes 1 and 2). Opening of the oxirane ring in **7** with secondary amines led to the formation of the desired compounds **8a-8b** (Scheme 2). Friedelcraft's acylation of **3** with maleic anhydride and chloracetyl chloride in the presence of aluminum chloride gave **9** and **10**, respectively. Esterification of **9** with a mixture of methanol and sulfuric acid furnished **9a** in good yield. However, esterification of **9** in the presence of methanol and boron trifluoride etherate yielded **9b**. Evidence for the structural assignment of **9b** was obtained by observing the nuclear Overhauser effect (NOE) and by carrying out decoupling experiments. Irradiation of methylene protons of the side chain at C-2 of **9b** led the vicinal methine proton to appear as a singlet. Similarly, during reverse decoupling experiments, irradiation of the methine proton made the adjacent methylene protons appear as singlet. Irradiation of methoxy protons at δ 3.32 ppm resulted in 15% enhancement of the integration count for the aromatic proton at C-3 in **9b**.

Ring closure of **10** in the presence of sodium acetate yielded **11** in good yield. Reaction of this furanone derivative with aromatic aldehydes furnished **12a-12b**, and the carbonyl group at C-20 did not participate in the reaction. The Dreiding model of these compounds indicated significant steric hindrance in Z-isomers and suggested that compounds **12a-12b** are E-isomers. This is in agreement with observations made earlier for other structurally related compounds.[6-8]

Regioselective reaction (Scheme 1) at C-20 was carried out by reacting **1** with triethylorthoformate in the presence of boron trifluoride etherate to yield **13**. The *cis* configuration of this compound was evident from the coupling constant (J = 6Hz) of the ethylenic protons. The *cis* geometry was possibly favored because it permitted intramolecular hydrogen bonding. Reductive amination of **1** with sodium cyanoborohydride in the presence of aluminum acetate in a mixture of methanol and tetrahydrofuran yielded **14**, and this reagent did not attack ring A. However, reductive amination was not stereospecific. Reaction of compound **14** with succinic anhydride gave the succinamic acid derivative **15**.

References

1. Schaison G, George M, Lestrat N, Reinberg A, Baulieu EE (1985). Effects of the antiprogesterone steroid RU-486 during midluteal phase in normal women. *J Clin Endocrinol Metab* **61**:484–489.
2. Moersch GW, Culburtson TP, Morrow DF, Wittle EL, Humphrey RR, Neuklis WA, Butler ME, Creger MM (1964). The synthesis and myotropic activity of 1-halo-4-methylestra-1,3,5(10)-trienes. *J Med Chem* **7**:741–748.
3. Preuss W (1981). Simplified degeneration of steroid C-22 carboxylic acid. *Eur Pat Appl* (CA **96**:181506 W) EP 41612.
4. Moersch GW, Neuklis WA, Culbertson TP, Morrow DF, Butler ME (1964). Preparation of steroidal 3-haloandrosta-1,3,5-trienes and 1-halo-4-methylestra-1,3,5(10)-trienes. *J Org Chem* **29**:2495–2499.
5. Sondheimer F, Valasco M, Rosenkranz G (1955). Synthesis of 1-dehydroprogesterone and 1-dehydro-17-ethinyltestosterone. *J Am Chem Soc* **77**:5673–5676.
6. Matsuda I, Murata S, Izumi Y (1979). A simple synthesis of α-ylidene-γ-lactones from γ-trimethylsiloxy nitriles. *Bull Chem Soc Jpn* **52**:2389–2393.
7. Tanaka K, Uneme H, Yamagishi N, Tanikaga R, Kaji A (1980). New methods for stereoselective synthesis of α-alkylidene-γ-butyrolactones. *Bull Chem Soc Jpn* **53**:2910–2916.
8. De D, Seth M, Bhaduri AP (1990). Regioselective borohydride and Grignard reactions in E-3-(arylmethylene)-4,5-dihydro-2(3H)-furanones. *Synthesis* **10**:956–959.