NOVEL AND REGIOSPECIFIC SYNTHESIS OF 2-AMINO ESTROGENS VIA ZINCKE NITRATION

Mitsuteru Numazawa and Katsuhiko Kimura

Tohoku College of Pharmacy
4-1 Komatsushima-4-chome, Sendai 983, Japan

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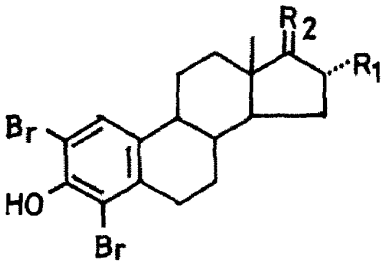
ABSTRACT

An efficient synthesis of 2-aminoestrone (14), 2-aminoestradiol (15), 2-amino-16α-hydroxyestrone (16) and 2-aminoestriol (17) is described. 2,4-Dibromo estrogens 1 - 4 were regiospecifically converted to the corresponding 2-nitro-4-bromo derivatives 5 - 8 in quantitative yields, with Zincke nitration using sodium nitrite. Catalytic hydrogenation of the 2-nitro-4-bromides 5 - 8 over palladium-on-charcoal gave directly the desired 2-amino estrogens 14 - 17 in high yields. The 2-amino compounds 15 and 17 were also obtained by the reduction of the corresponding 2-nitro-4-bromides 6 and 8 with sodium borohydride in the presence of palladium chloride.

INTRODUCTION

2-Amino estrogens are an important class of compounds for further synthetic elaboration. The 2-amino compounds can be converted to the halides [1-3], methoxides [4] and bis(2-chloroethyl)amines [5] which have interesting biological activities. Stubenrauch and Knuppen [6] reported oxidative hydrolysis of the amino compounds with sodium metaperiodate, yielding catechol estrogens. The amines, so far, have been obtained by reduction of the corresponding nitro compounds [1-6]. Nitration of estrogens with nitric acid produces usually an approximate 1:1 mixture of 2- and 4-nitro compounds, along with trace amounts of 2,4-dinitro derivatives. Very recently, Santaniello *et al.* [7] reported a regioselective nitration at the C-2 position of estrone with N-nitropyrazole but the yield is not satisfactory (40-45%).

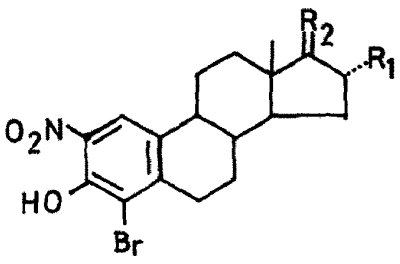


1 R_1 = H, R_2 = O

2 R_1 = H, R_2 = OH (H)

3 R_1 = OH, R_2 = O

4 R_1 = OH, R_2 = OH (H)

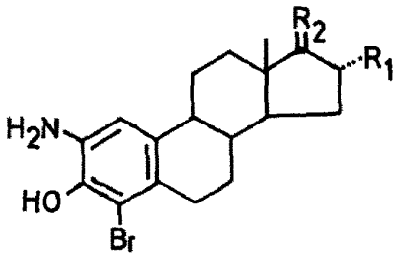


5 R_1 = H, R_2 = O

6 R_1 = H, R_2 = OH (H)

7 R_1 = OH, R_2 = O

8 R_1 = OH, R_2 = OH (H)

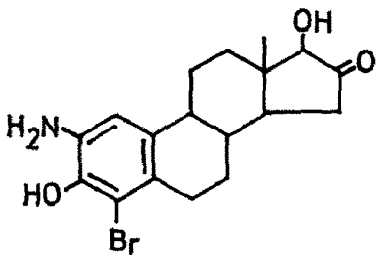


9 R_1 = H, R_2 = O

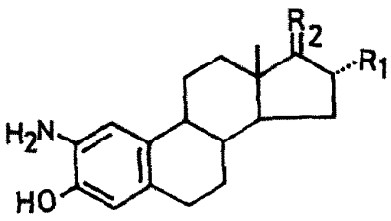
10 R_1 = H, R_2 = OH (H)

11 R_1 = OH, R_2 = O

12 R_1 = OH, R_2 = OH (H)



13



14 R_1 = H, R_2 = O

15 R_1 = H, R_2 = OH (H)

16 R_1 = OH, R_2 = O

17 R_1 = OH, R_2 = OH (H)

Zincke and others [8-10] proved that when a 2,6-dibrominated phenol or cresol is treated with nitrous acid, a bromine atom can be replaced by a nitro group in high yield. This paper describes a regiospecific and efficient synthesis of 2-amino estrogens, involving the Zincke nitration of 2,4-dibromo estrogens and subsequent hydrogenation over palladium-on-charcoal of the resulting 2-nitro-4-bromides.

RESULTS AND DISCUSSION

When 2,4-dibromoestrone (1) [11] was treated with 2 equivalents of sodium nitrite in acetic acid at room temperature for 30 min, surprisingly, 2-nitro-4-bromo compound 5 was regiospecifically obtained in quantitative yield without formation of the 4-nitro isomer. Dibromides 2, 3 and 4 [12,13] were quantitatively converted to the 2-nitro-4-bromo derivatives 6, 7 and 8 in a similar manner as above, respectively. The products were readily isolated in the pure form by crystallization. The C-2 position was assigned to the nitro group in these compounds on the basis of the chemical shift (7.9 - 8.0 ppm) of the C-1 proton in ^{1}HNMR spectra [6] and their structures were further determined by UV and IR spectra and elemental analysis.

To our knowledge, regiospecific Zincke nitration of 2,4-dibromo estratrienes has not previously been reported. Previously we demonstrated the regioselective hydrodebromination occurring at the C-2 position of the 2,4-dibromo compounds over palladium-on-charcoal [14]. The present results together with those of the catalytic hydrogenation clearly showed that the bromine atom at C-2 of the 2,4-dibromides is preferentially replaced by a nucleophile (*e. g.*, NO_2^-) or hydrogen.

Treatment of 2-nitro-4-bromo compounds 5, 6 and 8 with alkaline hydrosulfite essentially as described by Kraychy [4] gave the corre-

sponding 2-amino-4-bromo derivatives 9, 10 and 12 in high yields. On the other hand, the reduction of compound 7 having a 16α-hydroxy-17-keto structure by this method afforded the rearranged ketol 13 in place of compound 11. The structures of the 2-amino-4-bromides were identified by IR and ^{1}HNMR spectra and elemental analysis. Derivatives 9, 10 and 12 were efficiently hydrodebrominated over palladium-on-charcoal to yield the corresponding 2-amino estrogens 14, 15 and 17 which were identical with the authentic samples in every respect.

In order to obtain 2-amino estrogens directly from the 2-nitro-4-bromo derivatives produced above, we then explored reduction of the 2-nitro group and simultaneous removal of the 4-bromine atom. Treatment of the 2-nitro-4-bromides 6 and 8 with sodium borohydride in the presence of a transition metal [13], palladium chloride, gave 2-aminoestradiol (15) and 2-aminoestriol (17). Similar treatment of compounds 5 and 7 having a carbonyl group at C-17 afforded compounds 15 and 17. On the other hand, catalytic hydrogenation of compounds 5 - 8 over palladium-on-charcoal gave quantitatively the 2-amino estrogens 14 - 17, respectively. The IR and ^{1}HNMR spectra of the 2-amino estrogens supported their structures. The overall yields of the 2-amino derivatives from the starting primary estrogens were much improved (75-85%), compared to the reported ones (less than 40%) [1-6].

In addition to the very high yields, this synthetic method has advantages over the previous ones [1-6] in simplicity of handling and in avoiding the need of chromatographic separation of the products. It should also be noted that this procedure is suitable for the synthesis of 2-amino derivatives of 16α-hydroxylated estrogens, which could not be efficiently obtained by the previously reported methods [1-6].

EXPERIMENTAL

General methods. Melting points were measured on a Yanagimoto melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu 400 spectrophotometer in KBr pellets. UV spectra were obtained with a Shimadzu UV 300 spectrophotometer. ^{1}HNMR spectra were measured with a JEOL PMX 60 spectrometer at 60 MHz. Chemical shifts are reported in parts per million (δ) relative to Me_4Si. Mass spectra were taken on a Hitachi RMU-7L instrument. Rotations were obtained with a JASCO DIP-140 polarimeter.

Reaction of the 2,4-dibromides 1, 2, 3 and 4 with sodium nitrite in acetic acid. To a solution of 1, 2, 3 or 4 (2.32 mmol.) in AcOH (100 ml) was added 3.2 ml of a 10% aqueous solution of $NaNO_2$ and the mixture was stirred at room temperature for 30 or 60 min. The mixture was poured into water (500 ml) and then extracted with AcOEt (500 ml x 2). The organic layer was washed with a 5% $NaHCO_3$ solution and H_2O and dried (Na_2SO_4). After evaporation of the solvent the residue (850-930 mg) was obtained.

2-Nitro-4-bromo-3-hydroxy-1,3,5(10)-estratrien-17-one (5). The nitrated residue obtained from 1 (30 min of reaction time) was crystallized from acetone to give 5 (858 mg, 94%) as yellow needles, mp 136-137 °C. UV (MeOH): λ_{max} 298 (ε 6270). IR (KBr): ν_{max} 3400 (OH), 1735 (C=O), 1560 (NO_2). ^{1}HNMR ($CDCl_3$): δ 0.97 (3H, s, 18-CH_3), 8.00 (1H, s, 1-H). $[\alpha]_D^{22}$: +110.1°(c=1.0, $CHCl_3$).

Anal. Calcd. for $C_{18}H_{20}O_4NBr$: C, 54.84; H, 5.11; N, 3.55; Br, 20.27.
Found C, 54.60; H, 4.90; N, 3.34; Br, 20.51.

2-Nitro-4-bromo-1,3,5(10)-estratriene-3,17β-diol (6). The crude product obtained from 2 (30 min of reaction time) was crystallized from MeOH to give 6 (880 mg, 96%) as yellow needles, mp 196-198 °C. UV (MeOH): λ_{max} 298 (ε 5800). IR (KBr): ν_{max} 3400 (OH), 1560 (NO_2). ^{1}HNMR ($CDCl_3$): δ 0.76 (3H, s, 18-CH_3), 3.73 (1H, t J=7 Hz, 17α-H), 8.00 (1H, s, 1-H). $[\alpha]_D^{22}$: +60.5°(c=1.0, $CHCl_3$).

Anal. Calcd. for $C_{18}H_{22}O_4NBr$: C, 54.56; H, 5.60; N, 3.53; Br, 20.16.
Found C, 54.38; H, 5.53; N, 3.15; Br, 20.27.

2-Nitro-4-bromo-3,16α-dihydroxy-1,3,5(10)-estratrien-17-one (7). The crude nitrated product of 3 (30 min of reaction time) was crystallized from acetone to give 7 (914 mg, 95%) as yellow needles, mp 231-233 °C. UV (MeOH): λ_{max} 297 (ε 5740). IR (KBr): ν_{max} 3500 (OH), 1735 (C=O), 1560 (NO_2). ^{1}HNMR ($CDCl_3$): δ 0.97 (3H, s, 18-CH_3), 4.40 (1H, m, 16β-H), 8.00 (1H, s, 1-H). $[\alpha]_D^{22}$: +86.7° (c=1.0, $CHCl_3$).

Anal. Calcd. for $C_{18}H_{20}O_5NBr$: C, 52.70; H, 4.91; N, 3.41; Br, 19.50.
Found C, 52.43; H, 4.74; N, 2.99; Br, 19.16.

2-Nitro-4-bromo-1,3,5(10)-estratriene-3,16α,17β-triol (8). The crude nitrated product of 4 (60 min of reaction time) was crystallized from MeOH to give 8 (830 mg, 90%) as yellow needles, mp 248-250 °C. UV

(MeOH): λ_{max} 298 (ε 5540). IR (KBr): ν_{max} 3400 (OH), 1560 (NO_2). ^{1}HNMR (DMSO-d_6): δ 0.76 (3H, s, 18-CH_3), 3.33 (1H, d J=6 Hz, 17α-H), 3.90(1H, m, 16β-H), 7.90 (1H, s, 1-H). $[\alpha]_D^{22}$: +52.9°(c=0.41, $CHCl_3$).

Anal. Calcd. for $C_{18}H_{22}O_5NBr$: C, 52.44; H, 5.38; N, 3.40; Br, 19.38. Found C, 52.47; H, 5.47; N, 3.11; Br, 19.56.

Reduction of the 2-nitro-4-bromides 5-8 with sodium hydrosulfite. To a refluxing solution of the respective nitro compound (200 mg) in a mixture of 60 ml of acetone, 14 ml of H_2O and 12 ml of a 1N NaOH solution was added $Na_2S_2O_4$ (1.68 g) under vigorous stirring. The dark yellow color of the solution changed to light yellow after approx. 30 min. The mixture was diluted with H_2O (40 ml) and most of the acetone was removed under reduced pressure and then the solution was neutralized with a 10% AcOH solution. The white precipitate was filtered off, washed with H_2O and dried to give the crude 2-amino-4-bromo compound (170-185 mg).

2-Amino-4-bromo-3-hydroxy-1,3,5(10)-estratrien-17-one (9). The crude product obtained from 5 was crystallized from $CHCl_3$-MeOH to give 9 (172 mg, 95%) as colorless needles, mp 232-236 °C. UV (MeOH): λ_{max} 298 (ε 3450). IR (KBr): ν_{max} 3300-3400 (OH and NH_2), 1725 (C=O). ^{1}HNMR ($CDCl_3$-CD_3OD): δ 0.97 (3H, s, 18-CH_3), 6.73 (1H, s, 1-H). $[\alpha]_D^{20}$:+118.5° (c=1.0, $CHCl_3$).

Anal. Calcd. for $C_{18}H_{22}O_2NBr$: C, 59.35; H, 6.04; N, 3.85; Br, 21.93. Found C, 59.10; H, 6.11; N, 3.83; Br, 22.23.

2-Amino-4-bromo-1,3,5(10)-estratriene-3,17β-diol (10). The crude reduction product of 6 was crystallized from MeOH to give 10 (173 mg, 95%) as colorless needles, mp 210-211 °C. UV (MeOH): λ_{max} 298 (ε 3150). IR (KBr): ν_{max} 3400 (OH and NH_2). ^{1}HNMR ($CDCl_3$): δ 0.76 (3H, s, 18-CH_3), 3.73 (1H, t J=7 Hz, 17α-H), 6.73 (1H, s, 1-H). $[\alpha]_D^{20}$: +58.3°(c=1.0, $CHCl_3$).

Anal. Calcd. for $C_{18}H_{24}O_2NBr$: C, 59.02; H, 6.60; N, 3.82; Br, 21.85. Found C, 58.70; H, 6.53; N, 3.51; Br, 22.03.

2-Amino-4-bromo-1,3,5(10)-estratriene-3,16α,17β-triol (12). Crystallization of the crude product of 8 from MeOH yielded 12 (165 mg, 90%) as colorless needles, mp 159-161 °C. UV (MeOH): λ_{max} 298 (ε 3150). IR (KBr): ν_{max} 3400 (OH and NH_2). ^{1}HNMR ($CDCl_3$): δ 0.76 (3H, s, 18-CH_3), 3.34 (1H, d J=6 Hz, 17α-H), 3.90 (1H, m, 16β-H), 6.72 (1H, s, 1-H). $[\alpha]_D^{20}$: +52.9°(c=0.49, MeOH).

Anal. Calcd. for $C_{18}H_{24}O_3NBr$: C, 56.55; H, 6.33; N, 3.66; Br, 20.90. Found C, 56.33; H, 6.31; N, 3.52; Br, 20.77.

2-Amino-4-bromo-17β-hydroxy-1,3,5(10)-estratrien-16-one (13). The crude product obtained from 7 was crystallized from $CHCl_3$-MeOH to afford 13 (128 mg, 72%) as colorless needles, mp 273-277 °C. UV (MeOH): λ_{max} 297 (ε 3200). IR (KBr): ν_{max} 3400 (OH and NH_2), 1740 (C=O). ^{1}HNMR (CD_3OD): δ 0.77 (3H, s, 18-CH_3), 3.80 (1H, s, 17α-H), 6.73 (1H, s, 1-H). $[\alpha]_D^{20}$: +45.5° (c=0.41, MeOH).

Anal. Calcd. for $C_{18}H_{22}O_3NBr$: C, 56.86; H, 5.83; N, 3.68; Br, 21.01. Found C, 56.55; H, 5.80; N, 3.35; Br, 21.26.

Synthesis of 2-amino estrogens 14-17. (A) $NaBH_4$-$PdCl_2$ method: 2-Nitro-4-bromo compounds 5-8 (0.49 mmol.) were dissolved in MeOH (100 ml). To these solutions were added $PdCl_2$ (3.1 mmol.) and $NaBH_4$ (7.27 mmol.) and the mixtures were stirred under N_2 at 0 °C for 30 min. After this time, the reaction mixtures were filtered and the filtrates were condensed to approx. 10 ml and then diluted with AcOEt (50 ml). The organic layers were washed with H_2O and dried (Na_2SO_4). The crude residues (140-155 mg) were obtained after evaporation of the solvent.

(B) Catalytic hydrogenation with Pd/C: Mixtures of 0.50 mmol. of compounds 5-8, 100 ml of EtOH and 50 mg of 5% Pd/C were stirred under H_2 at room temperature and atmospheric pressure. After the reaction was complete (approx. 7-8 hr), the mixtures were filtered and the solvent evaporated to give the crude residues (151-165 mg).

2-Amino-3-hydroxy-1,3,5(10)-estratrien-17-one (14). Crystallization of the crude product obtained from 5 gave 14 (methods A and B: 90%) as colorless needles, mp 218-220 °C (decomp.) (lit. mp 215-218 °C (decomp.) [6], mp 220 °C (decomp.) [15]). ^{1}HNMR ($CDCl_3$): δ 0.97 (3H, s, 18-CH_3), 6.62 (1H, s, 4-H), 6.43 (1H, s, 1-H).

2-Amino-1,3,5(10)-estratriene-3,17β-diol (15). The crude reduced product of 6 was crystallized from acetone to yield 15 (method A: 95%, method B: 90%) as colorless needles, mp 196-198 °C (lit. [6] mp 193-196 °C). ^{1}H-NMR ($CDCl_3$): δ 0.76 (3H, s, 18-CH_3), 3.73 (1H, t J=7 Hz, 17α-H), 6.43 (1H, s, 4-H), 6.63 (1H, s, 1-H).

2-Amino-3,16α-dihydroxy-1,3,5(10)-estratrien-17-one (16). The crude reduced product of 7 was crystallized from $CHCl_3$-MeOH to give 16 (method B: 98%) as colorless needles, mp >300°C. IR (KBr): ν max 3300-3400 (OH and NH_2), 1725 (C=O). ^{1}HNMR ($CDCl_3$-CD_3OD): δ 0.97 (3H, s, 18-CH_3), 4.39 (1H, m, 16β-H), 6.43 (1H, s, 4-H), 6.63 (1H, s, 1-H). $[\alpha]_D^{20}$: +94.5° (c=1.0, MeOH).

Anal. Calcd. for $C_{18}H_{23}O_3N$: C, 71.74; H, 7.69; N, 4.62. Found C, 71.35; H, 7.58; N, 4.33.

2-Amino-1,3,5(10)-estratriene-3,16α,17β-triol (17). The crude residue obtained from 8 was crystallized from MeOH to yield 17 (method A: 94%, method B: 90%) as colorless needles, mp >300 °C. IR (KBr): ν max 3300-3400 (OH and NH_2). ^{1}HNMR ($CDCl_3$-CD_3OD): δ 0.76 (3H, s, 18-CH_3), 3.35 (1H, d J=6 Hz, 17α-H), 3.90 (1H, m, 16β-H), 6.45 (1H, s, 4-H), 6.66 (1H, s, 1-H). $[\alpha]_D^{22}$: +72.2° (c=0.41, MeOH).

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.26; H, 8.29; N, 4.61. Found C, 71.38; H, 8.15; N, 4.51.

ACKNOWLEDGMENT

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REFERENCES

The following trivial names have been used in this paper:

2-Aminoestrone= 2-amino-3-hydroxy-1,3,5(10)-estratrien-17-one
2-Aminoestradiol= 2-amino-1,3,5(10)-estratriene-3,17β-diol
2-Amino-16α-hydroxyestrone= 2-amino-3,16α-dihydroxy-1,3,5(10)-estratrien-17-one
2-Aminoestriol= 2-amino-1,3,5(10)-estratriene-3,16α,17β-triol
2,4-Dibromoestrone= 2,4-dibromo-3-hydroxy-1,3,5(10)-estratrien-17-one
Estrone= 3-hydroxy-1,3,5(10)-estratrien-17-one.

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