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Preparation of N-Aryl-2-hydroxypropionamides from Hydroxy Aromatic Compounds Using a One-Pot Smiles Rearrangement Procedure

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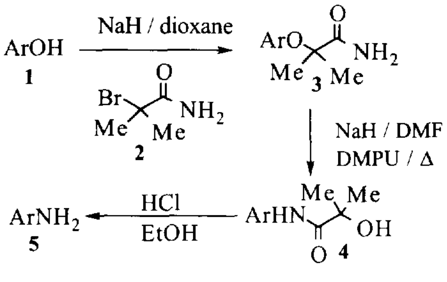
Abstract: Acylation of hydroxy aromatic compounds with 2-bromo-2-methylpropionamide followed by Smiles rearrangement of the resulting 2-aryloxypropionamide in a one-pot procedure produced the corresponding 2-hydroxy-2-methyl-N-arylpropionamides which can be converted to arylamines by hydrolysis. Particularly important applications of this new process were the conversions of estrone (**6**) and estradiol (**14**) to the corresponding 3-aminoestratriene derivatives **8** and **15**, respectively. In addition, an improved Semmler-Wolff procedure is described for the conversion of 19-nortestosterone (**22**) to 3-aminoestra-1,3,5(10)-trien-17β-ol hydrochloride (**26**). © 1997 Elsevier Science Ltd.

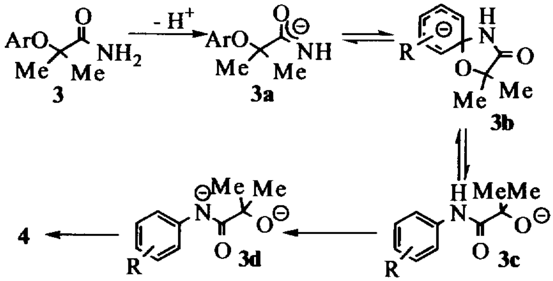
INTRODUCTION

Several methods have been developed for the conversion of phenols to anilines, since phenols are generally more available than the corresponding anilines. These methods include activation of the phenol with 4-chloro-2-phenylquinazoline[1-5] or diethyl chlorophosphate,[6] and the Bucherer reaction.[7-10] These methods all suffer from particular drawbacks. The sequence involving rearrangement of an aryloxyquinazoline and subsequent hydrolysis requires extremely high temperatures (ca. 300 °C) and basic conditions.[1-5] Preparation of the aryl diethyl phosphate esters involves the use of diethyl chlorophosphate, which is toxic, and potassium metal in liquid ammonia.[6] The Bucherer reaction[7-9] works best with naphthalenes and related heterocycles, e.g. hydroxyquinolines, whereas benzene derivatives are much less reactive.[10] In a variation of the Bucherer reaction using ammonia under pressure in the presence of zinc chloride as catalyst, 3-amino-2-naphthoic acid was prepared from the corresponding naphthol.[10]



Scheme I. Smiles Rearrangement

Another method which has been used for the conversion of hydroxy aromatic compounds to their corresponding amino compounds is an alkylation-rearrangement-hydrolysis sequence[11-13] which is a specific example of the Smiles rearrangement.[14-17] Alkylation of the hydroxy aromatic compound **1** (Scheme I) is performed with 2-bromo-2-methylpropionamide (**2**) to produce the 2-aryloxy-2-methylpropionamide **3**. Smiles rearrangement of **3** gives the isomeric, N-aryl-2-hydroxypropionamide **4**. Hydrolysis of amide **4** then gives the amino aromatic compound **5**. A mechanism for the Smiles rearrangement is presented in Scheme II.[11] Proton abstraction first produces the amide anion **3a** which can attack the aromatic nucleus to produce the spiro aromatic anion **3b**. Breaking of the carbon-nitrogen bond in **3b** regenerates anion **3a** in an unproductive process. However, breaking of the carbon-oxygen bond in **3b** is a productive process which leads to the alkoxide **3c**. Excess base can abstract the amide proton in **3c** to produce the dianion **3d** which can no longer return to **3b** because of unfavorable electronic interactions. Simple protonation of **3d** produces the Smiles rearranged product **4**.

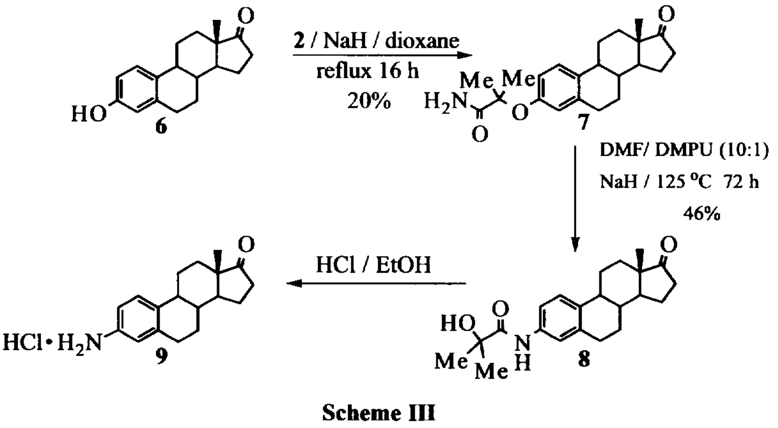


Scheme II. Mechanism of the Smiles Rearrangement[11]

We recently required 3-aminoestratrienes as starting materials for further elaboration. Since several 3-hydroxyestratrienes are commercially available, we chose to investigate a Smiles rearrangement process for converting selected 3-hydroxyestratrienes to the requisite 3-aminoestratrienes. This report describes a one-pot Smiles rearrangement procedure which we applied to the preparation of 3-aminoestratrienes and other aromatic amines.

RESULTS AND DISCUSSION

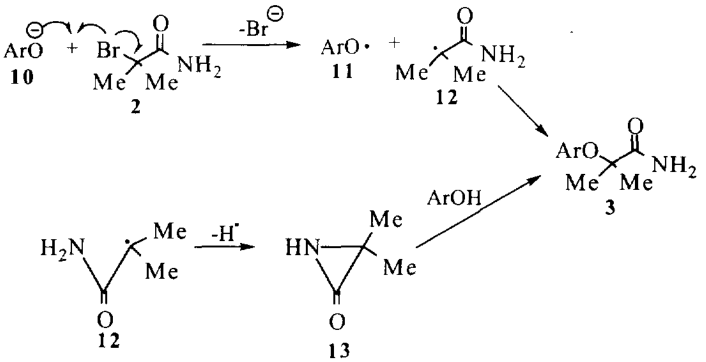
Our attempts to repeat the alkylation and Smiles rearrangement of estrone (**6**) to the acylated 3-aminosteroid **8** (Scheme III) as reported by Coutts and Southcott[13] met with limited success. In our hands, treatment of estrone (**6**) with sodium hydride and 2-bromo-2-methylpropionamide (**2**) in dioxane at reflux for 16 hours gave an approximate 1:1 mixture by NMR of unreacted estrone (**6**) and alkylated product **7**. Chromatography afforded pure **7** in only 20% yield. When 2-aryloxypropionamide **7** was treated with sodium hydride in 10:1 dimethylformamide (DMF):1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) at 125 °C for 72 hours, rearrangement product **8** was produced in a modest 46% yield. Thus, the overall yield of **8** was only 9% so we sought a more efficient procedure for accessing amino steroid **9**.



Scheme III

We considered ways in which we could change the reaction conditions to facilitate the probable mechanistic processes. With regard to the O-alkylation step, we felt that ionic processes were not feasible, since an SN1 mechanism would localize a carbocation, albeit tertiary, alpha to a carbonyl group; and an SN2 mechanism would involve the concerted displacement of a large halogen atom from an extremely hindered carbon center. Thus, we felt that a single electron transfer (SET) pathway was a potentially operative mechanistic process. Alkylation of phenols by a one-electron process has been documented.[18] In Scheme IV are shown two possible SET mechanisms. Disproportionation of bromo propionamide **2** in the presence of phenolate **10** could give aryloxy radical **11** plus the stabilized α-propionamide radical **12**. Combination of these two radicals would then produce the 2-aryloxypropionamide **3**.

Alternatively, the α-propionamide radical **12** could react intramolecularly with loss of a hydrogen radical as shown in Scheme IV to transiently produce the reactive aziridinone **13** from which the 2-aryloxypropionamide **3** could derive by reaction with a hydroxy aromatic compound. Indeed, Coutts and Southcott[13] have also suggested the intermediacy of aziridinone **13**.



Scheme IV

Since large transition metal cations are known to promote the SET pathway in Grignard additions,[19] we chose to explore the use of cesium carbonate in conjunction with sodium hydride in the alkylation of estrone (**6**) with 2-bromo-2-methylpropionamide (**2**). Treatment of estrone (**6**) with three equivalents each of sodium hydride, cesium carbonate and **2** in dioxane at reflux for 16 hours gave a 76% yield of the propionamide **7** after chromatography (Scheme III). The alkylation could not be effected with cesium carbonate alone.

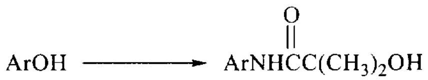
We next turned our attention to possible ways of improving the yield of the Smiles rearrangement step. It occurred to us that this rearrangement could be reversible and that in cases where rearranged product **4** and starting material **3** were both recovered from reaction mixtures, an equilibrium mixture may have developed. However, this possibility was ruled out, at least for one specific example, when 2-hydroxy-N-arylpropionamide **8** was recovered unchanged when resubjected to the rearrangement conditions of Scheme III for 16 hours. Thus, we set out to devise conditions for pushing the rearrangement more towards completion.

It seemed reasonable to assume that the rearrangement could be driven to completion by either increasing reaction time or temperature. A reaction time of 72 hours already seemed long, so we chose to increase the reaction temperature. Thinking that 125°C at extended time periods was approaching the practical limits of dimethylformamide, we chose to use the more stable cyclic analog of dimethylformamide, namely, N-methylpyrrolidinone (NMP).

We envisioned that the two-step alkylation-rearrangement process could be conducted in one pot. Estrone (**6**) was again treated with sodium hydride and cesium carbonate in dioxane and the resulting anion was treated with 2-bromo-2-methylpropionamide (**2**). When the alkylation was complete, more sodium hydride, NMP and DMPU were added and the bath temperature was raised to 150 °C. After 72 hours at 150 °C, the reaction was worked up and chromatographed to afford the rearrangement product **8** in 59% yield (71% based on recovered **6**). Thus, the overall yield for the preparation of **8** (Scheme III) was significantly better for the more convenient two-step, one-pot process (59%) than for the original two-step, two-pot process in our hands (9%).

Additional Smiles rearrangements were then conducted using the one-pot protocol. In Table I are listed the alkylations and rearrangements which we studied and the yields in which these one-pot conversions proceeded. In some cases, as indicated, the starting hydroxy aromatic compound was recovered. In most cases, the yields were moderate to good. An exception was the conversion of estradiol (**14**) to the alkylated and rearranged product **15**, which occurred in only 23% yield. The use of 4-ethoxyphenol (**16**) demonstrates that a precursor to phenacetin can be efficiently prepared using this procedure. The last entry in Table I, namely, the conversion of 2-hydroxydibenzofuran (**20**) to the alkylated and rearranged product **21**, is significant in that Coutts and Southcott[13] reported this synthesis as a two-step, two-pot process which proceeded in only 9% yield. Thus, this latter conversion is truly more efficient in addition to being simpler than the reported procedure.

Table I. Two-Step, One-Pot Alkylations and Smiles Rearrangements[a]



$$\mathrm{ArOH} \longrightarrow \mathrm{ArNH\overset{\overset{\displaystyle O}{\|}}{C}C(CH_3)_2OH}$$

Starting Material	Product	%Yield
estrone (**6**)	**8**	59[b]
estradiol (**14**)	**15**	23[c]
4-ethoxyphenol (**16**)	**17**[d]	65
2-naphthol (**18**)	**19**	72
2-hydroxydibenzofuran (**20**)	**21**	58[e]

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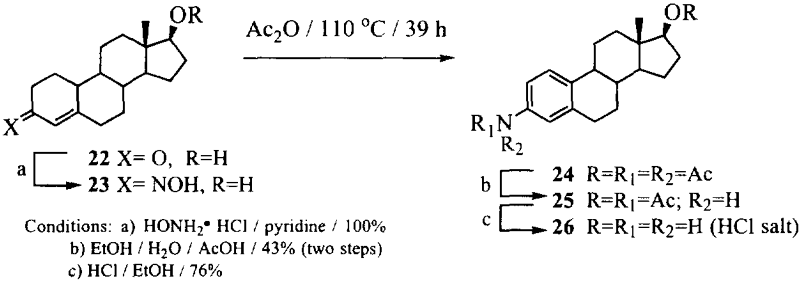
a. All new compounds were completely characterized. b. An 18% yield of estrone (**6**) was recovered by chromatography. c. A 12% yield of estradiol (**15**) was recovered by chromatography. d. Compound **17** is a precursor to phenacetin. e. In the two-step process reported by Coutts and Southcott (reference 13), the overall yield of **21** is only 9%.

Since the access to 3-aminoestratrienes was a particular goal of this work, we investigated other routes to these compounds as well. We have repeated and improved a Semmler-Wolf rearrangement process reported by Smith and Sant.[20] The preparation of 3-aminoestratriene derivative **26** from 19-nortestosterone (**22**) using this improved procedure is shown in Scheme V. The conversion of 19-nortestosterone (**22**) to **25** was performed as described by Smith and Sant.[20] We have significantly improved the preparation of 3-aminoestratriene **26** from **25**. Hydrolysis of both the N-acetyl and O-acetyl groups in **25** with ethanolic hydrochloric acid gave a 76% yield of the 3-aminoestratriene hydrochloride salt **26** which crystallized directly from the reaction solution. The clear advantage of this procedure over that reported by Smith and Sant[20] is in the isolation of the amine as a salt. Smith and Sant[20] isolated the free base of **26** as a "dark glass" in 45% yield which was "difficult to purify by recrystallization." Previous workers had also been unable to purify this free base.[21]



Conditions: a) $HONH_2 \cdot HCl$ / pyridine / 100%
b) EtOH / H_2O / AcOH / 43% (two steps)
c) HCl / EtOH / 76%

Scheme V

In summary, we have described a two-step, one-pot alkylation and Smiles rearrangement procedure for the conversion of hydroxy aromatic compounds to amino aromatic compounds. Both estrone (**6**) and estradiol (**14**) are substrates for this new procedure, and afford the corresponding 3-aminoestratriene derivatives **8** and **15**, respectively. Additional examples of this two-step, one-pot rearrangement procedure, which will further define the scope, will be the subject of a subsequent report.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Tlc analyses were performed with EM Science silica gel 60 F_{254} plates, with visualization by UV irradiation. Flash chromatography was performed with EM Separations silica gel 60 (0.040-0.063 mm). The NMR spectra were recorded on a Varian VXR 300, Gemini-300 or EM-390 spectrometer. The IR spectra were recorded on a Perkin-Elmer Model 1800 or Mattson Galaxy 5020 FT-IR spectrophotometer. The MS data were collected on a Finnigan MAT 4600 or MAT TSQ-700 spectrometer. Steroids were purchased from Berlichem; other reagents were purchased from Aldrich Chemical Company.

2-Bromo-2-methylpropionamide (**2**).

To a vigorously stirring mixture of 42.0 g (0.180 mole) of bromoisobutyryl bromide and 500 ml of hexane at 0°C was added 80 ml of concentrated aqueous ammonium hydroxide in portions over a 30-minute period. After an additional 30 minutes of stirring at 0°C, the resulting white precipitate was collected, washed with cold water and air-dried. Crystallization from chloroform-hexane (200 ml-20 ml) afforded 31.2 g (100%) of **2** as shiny white plates, m.p. 146-148°C (lit.[13] m.p. 147-148°C).

2-Methyl-2-[(17-oxoestra-1,3,5(10)-trien-3-yl)oxy]propionanide (**7**).

To a solution of 5.00 g (18.5 mmoles) of estrone (**6**) in 100 ml of dioxane was added 0.90 g (22.5 mmoles) of sodium hydride (60% dispersion in mineral oil). After 1 hour at reflux, the mixture was cooled to room temperature and treated with 3.70 g (22.2 mmoles) of 2-bromo-2-methylpropionamide (**2**). After 16 hours at reflux, the mixture was concentrated and the residue was partitioned between 1N sodium hydroxide solution (100 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (2 x 200 ml) and the combined organic layers were washed with 1N sodium hydroxide solution (100 ml), water (100 ml), dried (sodium sulfate) and concentrated to leave 6.6 g of material which appeared by NMR analysis to be a 1:1 mixture of **6**:**7**. Chromatography (9:1 to 2:3 to 1:1::hexane:ethyl acetate) gave 1.30 g (20%) of **7**, m.p. 158-160°C (lit.[13] m.p. 167-168°C); IR (KBr): 3491 (NH), 1737 (ester C=O), 1703 (ketone C=O) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 7.19 (d, 1H, J=8.7 Hz, C1-H), 6.74 (dd, 1H, J=8.7, 2.8 Hz, C2-H), 6.68 (d, 1H, J=2.8 Hz, C4-H), 6.65 (br s, 1H, NH_2), 5.57 (br s, 1H, NH_2), 2.90-2.85 (m, 2H, C6-H), 2.56-1.93 (m, 6H), 1.68-1.40 (m, 6H), 1.53 [s, 6H, $C(CH_3)_2$], 0.91 (s, 3H, C18-CH_3); ^{13}C NMR (deuteriochloroform): δ 220.7, 177.8, 152.1, 137.6, 134.7, 126.1, 121.1, 118.4, 81.0, 50.4, 47.9, 44.0, 38.2, 35.8, 31.5, 29.5, 26.4, 25.8, 25.0, 24.9, 21.5, 13.8; MS (chemical ionization, ammonia): m/e 373 (M + NH_4^+).

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.19; H, 8.34; N, 3.84.

2-Hydroxy-2-methyl-N-(17-oxoestra-1,3,5(10)-trien-3-yl)propionamide (**8**).

To a solution of 800 mg (2.25 mmoles) of **7** in DMF (10 ml) and 1,3-dimethyl-3,3,4,5,6,-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (1 ml) was added 100 mg (2.48 mmoles) of sodium hydride (60% dispersion in oil). The resulting solution was stirred at 125°C for 72 hours, cooled and partitioned between water (300 ml) and ethyl acetate (400 ml). The aqueous phase was extracted with ethyl acetate (400 ml) and the combined organic extracts were washed with water (3 x 200 ml), dried (sodium sulfate) and concentrated to leave ca. 0.5 g of brown oil. Chromatography (7:3:hexane:ethyl acetate) gave 0.31 g (46%) of **8** as a white solid, m.p. 159-160°C; m.p. 160-161°C (cyclohexane/ether) (lit.[13] m.p. 133-134°C).

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.26; H, 8.40; N, 3.80.

One-Pot Conversion of Estrone (**6**) to **8**.

To a solution of 1.00 g (3.70 mmoles) of estrone (**6**) in dioxane (20 ml) was added 300 mg (12.5 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. After 30 minutes of stirring at room temperature, 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide (**2**) was added and the mixture was heated at reflux for 16 hours. After the reflux period, N-methyl-2-pyrrolidone (NMP) (20 ml), DMPU (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was stirred at 150°C (oil bath temperature) for 72 hours. The mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave ca. 3 g of material. The brown oil was chromatographed (7:3::hexane:ethyl acetate) to give 770 mg (59%) of **8** as an off-white solid, m.p. 159-160°C (lit.[13] m.p. 133-134°C); IR (KBr): 3840 (OH), 3387 (NH), 1724 (ester C=O), 1686 (ketone C=O) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 8.60 (br s, 1H, NH), 7.44 (d, 1H, J=2.0 Hz, C4-H), 7.27-7.21 (m, 2H, C1-H and C2-H), 2.90 (dd, 2H, J=9.1, 4.3 Hz, C6-H_2), 2.56-1.93 (m, 8H), 1.70-1.40 (m, 6H), 1.54 [s, 6H, $C(CH_3)_2$], 0.90 (s, 3H, C18-CH_3); ^{13}C NMR (deuteriochloroform): δ 221.0, 174.1, 137.3, 135.9, 135.3, 125.8, 199.9, 117.1, 74.2, 50.4, 48.0, 44.1, 38.2, 35.8, 31.5, 29.5, 27.9, 26.4, 25.7, 21.6, 13.8; MS (chemical ionization, ammonia): m/e 373 ($M + NH_4^+$).

Also recovered from chromatographic purification of **8** was 180 mg (18%) of estrone (**6**). Yield of **8** based on recovered **6** was 71%.

One-Pot Conversion of Estradiol (**14**) to 2-Hydroxy-N-(17-hydroxyestra-1,3,5(10)-trien-3-yl)-2-methylpropionamide (**15**).

To a solution of 1.00 g (3.67 mmoles) of estradiol (**14**) in dioxane (20 ml) was added 400 mg (16.7 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide (**2**) was added and the resulting mixture was heated at reflux for 16 hours. After the reflux period, NMP (20 ml), DMPU (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was stirred and heated at 150°C for 72 hours. The mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave ca. 3 g of residue. Chromatography (7:3::hexane:ethyl acetate) gave 120 mg (12%) of recovered estradiol (**14**) followed by 100 mg (10%) of 3-amino-1,3,5(10)-estratrien-17β-ol as an off-white solid, m.p. 75-77°C (lit.[20] m.p. 143°C); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 6.90 (d, J=8.2 Hz, 1H, C1-H), 6.33 (dd, J=8.2, 2.5 Hz, 1H, C2-H), 6.25 (d, J=2.5 Hz, C4-H), 4.70 (br s, 2H, NH_2), 4.47 (d, J=4.9 Hz, 1H, C17-H), 3.55-3.47 (m, 1H), 2.68-2.62 (m, 2H, C6-H_2), 2.23-1.72 (m, 5H), 1.62-1.52 (m, 1H), 1.42-1.03 (m, 7H), 0.66 (s, 3H, C18-CH_3); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 145.9, 136.2, 127.6, 125.5, 113.9, 111.9, 80.0, 49.5, 43.6, 42.8, 36.6, 29.9, 29.2, 27.1, 26.1, 22.8, 11.3; MS (electron impact): m/e 271 (molecular ion).

A column flush with ethyl acetate (700 ml) afforded 300 mg (23%) of **15** as a brown semi-solid which was recrystallized from toluene to give an off-white powder, m.p. 175-177°C; m.p. 179-181°C (ethanol/cyclohexane) (lit.[13] m.p. 203-204°C); IR (KBr): 3376 (OH), 3322 (NH), 1665 (C=O) cm^{-1}; ^{1}H NMR (deuteriochloroform plus a few drops of dimethyl sulfoxide-d_6): δ 8.73 (br s, 1H, NH), 7.35-7.15 (m, 3H, aromatic), 4.49 (br s, 1H, OH), 3.65 (t, J=8.9 Hz, 1H, C17-H), 2.81-2.76 (m, 2H, C_6-H_2), 2.34-1.78 (m, 6H), 1.66-1.08 (m, 8H), 1.44 [s, 6H, $C(CH_3)_2$], 0.71 (s, 3H, C18-CH_3); ^{13}C NMR (deuteriochloroform plus a few drops of dimethyl sulfoxide-d_6): δ 174.9, 137.2, 136.1, 135.2, 125.6, 119.6, 116.8, 81.4, 73.4, 49.9, 44.0, 43.0. 38.5, 36.6, 30.2, 29.5, 27.6, 27.0, 26.0, 22.9, 11.0.

Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 73.50; H, 9.08; N, 3.86.

One-Pot Conversion of 4-Ethoxyphenol (**16**) to 2-Hydroxy-N-(4-ethoxyphenyl)-2-methylpropionamide (**17**).

To a solution of 511 mg (3.70 mmoles) of 4-ethoxyphenol in 20 ml of dioxane was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred at room temperature for 30 minutes, 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide (**2**) was added, and the resulting mixture was heated at reflux for 16 hours. After the reflux period, NMP (20 ml), DMPU (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the resulting mixture was heated and stirred at 150°C for 72 hours. The reaction mixture was cooled to room temperature and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave ca. 2 g of residue. Chromatography (7:3::hexane:ethyl acetate) gave 536 mg (65%) of **17** as an off-white solid, m.p. 146-148°C; IR (KBr): 3281 (OH), 3256 (NH), 1647 (C=O) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 8.59 (br s, 1H, NH), 7.45 (dd, J=9.0, 2.2 Hz, 2H, aromatic), 6.84 (dd, J=9.0, 2.2 Hz, 2H, aromatic); 4.00 (q, J=7.1 Hz, 2H, OCH_2), 2.73 (br s, 1H, OH), 1.53 [s, 6H, $C(CH_3)_2$], 1.39 (t, J=7.1 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (deuteriochloroform): δ 174.0, 155.7, 130.6, 74.0, 63.7, 27.9, 14.8; MS (chemical ionization, methane): m/e 224 (M^+ + 1).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.16; H, 7.47; N, 6.07.

One-Pot Conversion of 2-Naphthol (**18**) to 2-Hydroxy-N-(2-naphthyl)-2-methylpropionamide (**19**).

To a solution of 533 mg (3.70 mmoles) of 2-naphthol (**18**) in 20 ml of dioxane was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. After 30 minutes of stirring, 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide (**2**) was added and the mixture was heated at reflux for 16 hours. After the reflux period, NMP (20 ml), DMPU (2 ml) and 100 mg (4.07 mmoles) of dry sodium hydride were added and the mixture was stirred at 150°C for 72 hours. The reaction mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave ca. 3 g of material. The brown oil was chromatographed (7:3::hexane:ethyl acetate) to give 607 mg (72%) of **19** as an off-white solid, m.p. 155-157°C (lit.[13] m.p. 159-160°C); IR (KBr): 3289 (NH and OH), 1655 (C=O) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 9.74 (br s, 1H, NH), 8.41 (d, J=2.2 Hz, 1H, C1-H), 7.86-7.76 (m, 4H), 7.49-7.37 (m, 2H), 5.80 (br s, 1H, OH), 1.40 [s, 6H, $C(CH_3)_2$]; ^{13}C NMR (dimethyl sulfoxide-d$_6$): δ 175.7, 136.2, 133.3, 129.8, 128.1, 127.4, 127.3, 126.3, 124.6, 120.6, 115.6, 72.5, 27.7; MS (chemical ionization, ammonia): m/e 247 (M + NH_4^+).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 72.97; H, 6.57; N, 5.89.

One-Pot Conversion of 2-Hydroxydibenzofuran (**20**) to 2-Hydroxy-N-(2-dibenzofuranyl)-2-methylpropionamide (**21**).

To a solution of 682 mg (3.70 mmoles) of 2-hydroxydibenzofuran (**20**) in 20 ml of dioxane was added 300 mg (12.2 mmoles) of dry sodium hydride and 4.00 g (12.2 mmoles) of cesium carbonate. The mixture was stirred for 30 minutes, 2.03 g (12.2 mmoles) of 2-bromo-2-methylpropionamide (**2**) was added and the mixture was heated at reflux for 18 hours. After the reflux period, NMP (20 ml), DMPU (2 ml) and 100 mg (4.07

mmoles) of dry sodium hydride were added and the mixture was stirred and heated at 150°C for 72 hours. The mixture was cooled and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic extracts were washed with water (2 x 50 ml), dried (sodium sulfate) and concentrated to leave ca. 3 g of material. The brown oil was chromatographed (7:3::hexane:ethyl acetate) to give 580 mg (58%) of **21** as an off-white solid, m.p. 134-137°C (toluene); m.p. 159-161°C (cyclohexane) (lit.[13] m.p. 165-166°C); IR (KBr): 3383 (OH), 3364 (NH), 1668 (C=O) cm^{-1}; ^1H NMR (deuteriochloroform): δ 8.83 (br s, 1H, NH), 8.41 (d, J=2.3 Hz, 1H, C1-H), 7.92 (m, 1H, aromatic), 7.56-7.29 (m, 5H, aromatic), 2.46 (br s, 1H, OH), 1.60 [s, 6H, $C(CH_3)_2$]; ^{13}C NMR (deuteriochloroform): δ 174.2, 156.8, 152.9, 132.8, 127.3, 124.6, 124.2, 122.7, 120.8, 119.5, 112.0, 111.7, 74.3, 28.0; MS (electron impact): m/e 269 (molecular ion).

Anal. Calcd. for $C_{16}H_{15}NO_3$; C, 71.36; H, 5.61; N, 5.20. Found: C, 71.43; H, 5.58; N, 5.06.

17-Hydroxyestr-4-en-3-one Oximes (**23**).

A mixture of 41.5 g (0.150 mole) of 19-nortestosterone (**22**), 40.0 g (0.576 mole) of hydroxylamine hydrochloride, 400 ml of pyridine and 400 ml of ethanol was heated at reflux for 4 hours. The solvent was removed under reduced pressure and the residue was triturated with water to give 43.4 g (100%) of a mixture of *syn* and *anti* oximes **19** as a pink solid;[20] ^1H NMR (dimethyl sulfoxide-d_6): δ 6.4 and 5.8 (2s, 1H, *syn* and *anti* C4-H), 3.4 (t, 1H, C17-H), 2.8 and 2.4 (2 m, 1H, *syn* and *anti* C2-H), 2.1-0.8 (m, 17H, steroid envelope), 0.7 (s, 3H, C18-CH_3); MS (chemical ionization, ammonia): 290 (MH^+).

3-Acetylaminoestra-1,3,5(10)-trien-17β-ol (**25**).

A mixture of 38.0 g (0.131 mole) of oximes **23** and 750 ml of acetic anhydride was stirred under a nitrogen atmosphere at 110°C for 39 hours. Excess acetic anhydride was removed at reduced pressure to provide crude 3-diacetylamino-1,3,5(10)-estratrien-17β-ol acetate (**24**) as a dark, oily material which was used as such. A solution of crude **24** in ethanol (400 ml), water (200 ml) and acetic acid (20 ml) was heated at reflux for 15 hours and concentrated under reduced pressure to give a brown, oily residue, which was reconstituted in 300 ml of hot methanol and concentrated to 200 ml. Upon cooling, crystallization commenced to give 21.7 g (46%) of **25**. Recrystallization from methanol (1100 ml) gave 20.3 g (43%) of **25**, m.p. 209-210°C (lit.[20] m.p. 250°C); ^1H NMR (dimethyl sulfoxide-d_6): δ 9.7 (s, 1H, NH), 7.3-7.1 (m, 3H, aromatic), 4.6 (t, 1H, C17-H), 2.7 (m, 2H, C6-H_2), 2.3 (m, 1H, C9-H), 2.2-1.2 (m, 12H, steroid envelope), 2.0 (s, 6H, both $COCH_3$ groups), 0.8 (s, 3H, C18-CH_3); MS (chemical ionization, ammonia): m/e 356 (MH^+).

3-Aminoestra-1,3,5(10)-trien-17β-ol Hydrochloride (**26**).

A mixture of 40.0 g (0.113 mole) of amide **25**, 1 l of ethanol and 1 l of 6M hydrochloric acid was heated at reflux for 5 hours. Solution occurred initially and after ca. 3 hours product started to crystallize from the reaction solution. The mixture was cooled to 4°C for 15 hours and the solid was collected and washed with cold ethanol to give 26.7 g (76%) of **26**, m.p. >300°C (dec.); ^1H NMR (dimethyl sulfoxide-d_6): δ 7.4-7.0 (m, 3H, aromatic), 3.5 (t, 1H, C17-H), 2.8 (m, 2H, C6-H_2), 2.3-1.0 (m, 13H, steroid envelope), 0.6 (s, 3H, C18-CH_3); MS (chemical ionization, ammonia): m/e 272 (MH^+).

Anal. Calcd. for $C_{18}H_{25}NO{\bullet}HCl$: C, 70.22; H, 8.51; N, 4.55. Found: C, 70.20; H, 8.38; N, 4.39.

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