$$\delta(^{15}N)(I, Me_2CO) = (9.7 \pm 0.6)\sigma_F + (26.7 \pm 1.0)\sigma_R + (25.8 \pm 3.1)\Delta\sigma_R - 57.9 \pm 0.3 \text{ ppm}$$

$$n = 13 \text{ (all substituents)}, r = 0.998, \text{sd} = 0.4 \quad (3)$$

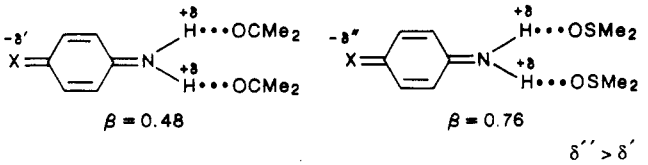
to be noted that eq 1 and 3 are consistent in that the intercept and the coefficients to σ_F and σ_R are the same within the errors of the estimates.

The $\delta(^{15}N)$ values of I in dimethyl sulfoxide were found in the previous study[3] to be well correlated by eq 4, which has the same form as eq 3.

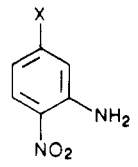
$$\delta(^{15}N)(I, Me_2SO) = (11.8 \pm 0.9)\sigma_F + (31.1 \pm 1.5)\sigma_R + (37.4 \pm 4.3)\Delta\sigma_R - 53.0 \pm 0.4 \text{ ppm}$$

$$n = 13, r = 0.998, \text{sd} = 0.7 \text{ ppm} \quad (4)$$

It is important to note that the value (25.8 ± 3.1) of ρ_S (dependence on $\Delta\sigma_R$) for ^{15}N chemical shifts in acetone solution (eq 3) is smaller by a factor of about 1.5 than that (37.4 ± 4.3) for the $\delta(^{15}N)$ shifts in dimethyl sulfoxide solution (eq 4). The smaller response in acetone is due to diminished π-electron-acceptance from the amino group that results from the approximately 1.5 factor weaker hydrogen-bond-acceptor (HBA) ability of acetone (HBA parameter $\beta_1 = 0.48$) than that of dimethyl sulfoxide ($\beta_1 = 0.76$).[6] With decreased HBA ability, the delocalization of π electrons from the hydrogen-bonded NH_2 to the conjugated para π-electron-acceptor substituent is reduced. The reduction of the SSAR effects in acetone solution can be expressed by the following forms:



A further test of the SSAR effect treatment has been carried out for the $\delta(^{15}N)$ of 5-substituted 2-nitroanilines



II

II in which the NH_2 detection center is in the nonconjugated meta position. The correlations of $\delta(^{15}N)$ (in Me_2SO 1.7 M solution) with σ_F, σ_R, and $\Delta\sigma_R$ are as follows.

$$\delta(^{15}N)(II, Me_2SO) = (7.4 \pm 0.4)\sigma_F - (1.4 \pm 0.6)\sigma_R - 34.6 \pm 2 \text{ ppm} \quad (5)$$

$$n = 9 \text{ (all substituents)}, r = 0.990, \text{sd} = 0.3 \text{ ppm}$$

$$\delta(^{15}N)(II, Me_2SO) = (7.2 \pm 0.4)\sigma_F - (1.9 \pm 0.7)\sigma_R + (2.3 \pm 2.1)\Delta\sigma_R - 34.7 \pm 0.2 \text{ ppm} \quad (6)$$

$$n = 9 \text{ (all substituents)}, r = 0.992, \text{sd} = 0.3 \text{ ppm}$$

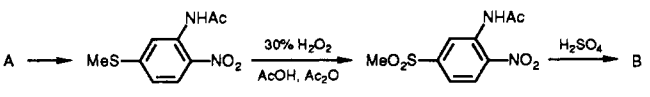
In eq 6 the ρ_s coefficient (2.3 ± 2.1) is not truly statistically significant, and eq 5 is the preferred one. The insignificant ρ_s coefficient (in marked contrast to the ρ_s value of 23.5 in eq 7 of our previous study[3] with 4-substituted 2-nitroanilines) can be accounted for by the absence of direct resonance interactions between the NH_2 detection center and the meta substituents.

This work together with our earlier report has provided confirmation that SSAR effects are generally applicable to physical as well as chemical properties and that results similar to the present ones are to be expected, for example, for $\delta(^{17}O)$ shifts of meta- and para-substituted phenols and (particularly) phenoxides.

Registry No. I (X = OCH_3), 104-94-9; I (X = CH_3), 106-49-0; I (X = F), 371-40-4; I (X = Cl), 106-47-8; I (X = CF_3), 455-14-1; I (X = SCF_3), 372-16-7; I (X = H), 62-53-3; I (X = CO_2CH_3), 619-45-4; I (X = $CO_2C_2H_5$), 94-09-7; I (X = $COCH_3$), 99-92-3; I (X = CN), 873-74-5; I (X = SO_2CH_3), 5470-49-5; I (X = NO_2), 100-01-6; II (X = OCH_3), 16133-49-6; II (X = CH_3), 578-46-1; II (X = F), 2369-11-1; II (X = CF_3), 402-14-2; II (X = H), 88-74-4; II (X = $CO_2C_2H_5$), 84228-43-3; II (X = $COCH_3$), 79127-41-6; II (X = SO_2CH_3), 121444-20-0; II (X = NO_2), 619-18-1; A, 23153-09-5; *N*-acetyl-2-nitro-5-(methylthio)aniline, 54029-49-1.

(6) Kamlet, M. J.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877.

(7) 5-(Methylsulfonyl)-2-nitroaniline (B) (mp 179.0–179.5 °C) was prepared as follows from 5-(methylthio)-2-nitroaniline (A), obtained as reported by Hodgson et al. (Hodgson, H. H.; Handley, F. W. *J. Chem. Soc.* **1928**, 162) from *m*-dichlorobenzene:



B	N	C	H	*m/l*
Anal. found	12.97	39.19	3.70	216
calcd	12.96	38.89	3.73	216.21

Synthesis of 3-Methoxyestra-1,3,5(10),6-tetraen-17-one

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In connection with our studies of dye-sensitized photooxygenation of styrenic estrogens,[1] we required a method for preparation of the title compound (**5**).

The schemes previously reported for the synthesis of 6-dehydroestrogens either give very low yields[2] or involve complex procedures.[3]

We now report efficient synthesis of **5** from 17β-hydroxyestr-4-en-3-one (**1**) via introduction of the Δ^6 double bond and selective microbial aromatization of ring A in two consecutive steps.

Oxidation of **1** with chromium(VI) oxide in acetic acid[4] followed by treatment of the resulting diketone **2** with chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) in ethanol[5] afforded, after column chromatography and crystallization, **3** in 41% yield from **1**. Attempted aromatization of ring A with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) led to complex mixtures, while treatment of **3** with iodine

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(3) (a) Masanobu, S.; Murakami, W.; Ueno, K.; Sakakibara, K. Japan Patent 75 21472, 1975; *Chem. Abstr.* **1976**, *84*, 74523. (b) Kaufmann, S.; Pataki, J.; Rosenkranz, G.; Romo, J.; Djerassi, C. *J. Am. Chem. Soc.* **1950**, *72*, 4531.

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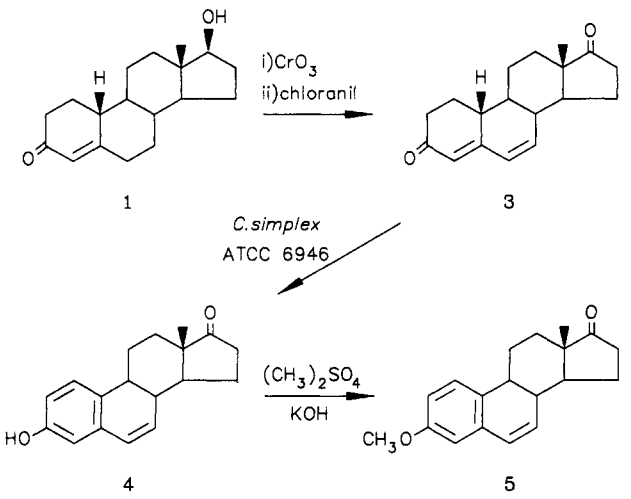
0022-3263/89/1954-3984$01.50/0

Scheme I



in pyridine, via the procedure reported by Alvarez and Watt,[6] gave **4** in only 3% yield.

Previous workers[7] had already shown that *Corynebacterium simplex* could be used to effect aromatization by the microbial dehydrogenation of certain 19-nor-Δ^4-3-ketosteroids. When **3** was submitted to this transformation, the phenol **4**, equal in all aspects to authentic sample, was isolated in 74% yield. Finally **4** was reacted to dimethyl sulfate and potassium hydroxide in aqueous methanol to give, after crystallization from ethanol, 90% of pure **5**.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 683 instrument. Ultraviolet spectra were measured in ethanol on a Hewlett-Packard 8450A spectrophotometer. ^{1}H NMR spectra were run at 80.131 MHz on a Bruker AC-80 spectrometer with $CDCl_3$ as a solvent. The chemical shifts are reported in δ values relative to tetramethylsilane, which was used as internal standard. Mass spectra were obtained through electron-impact ionization on a Hewlett-Packard 5995A instrument.

Analytical thin-layer chromatography (TLC) was performed on plates of Polygram Sil N-HR/UV_{254} (Macherey-Nagel) with a thickness of 0.20 mm silica gel.

Estr-4-ene-3,17-dione (2). To a solution of 17β-hydroxyestr-4-en-3-one (**1**) (6.17 g, 22.5 mmol) in acetic acid (300 mL) was added chromium(VI) oxide (1.70 g, 17.0 mmol) dissolved in acetic acid 96% (150 mL), and the solution was stirred at ambient temperature for 1 h. The reaction mixture was concentrated under vacuum to half of its initial volume, poured into 1 M hydrochloric acid (300 mL), and extracted with ethyl acetate (3 × 400 mL). The combined organic extracts were washed with saturated solution of $NaHCO_3$ and water and then dried over $MgSO_4$. Evaporation of solvent gave **2** (5.88 g, 96%), mp 165–168 °C (lit.[4] mp 169–171 °C).

Estra-4,6-diene-3,17-dione (3). A solution of **2** (4.10 g, 15.1 mmol) and chloranil (2.75 g, 11.2 mmol) in dry ethanol (400 mL) was stirred at 50 °C for 2 h and then evaporated under reduced pressure. The residue was triturated with chloroform (80 mL), and the mixture was allowed to stand overnight. The solid was removed by filtration, the filtrate was evaporated to dryness and redissolved in ethanol (400 mL), and the above procedure was repeated. The final residue from the evaporation of the chloroform was adsorbed onto basic alumina (100 g) and eluted with chloroform. Evaporation of the solvent afforded the crude dienone **3** (2.30 g), which was crystallized from acetone–petroleum ether to give a sample (1.75 g, 43%) of mp 177–180 °C (lit.[6] mp 180–182 °C).

3-Hydroxyestra-1,3,5(10),6-tetraen-17-one (4). *C. simplex* (ATCC 6946), conserved at 4 °C in agar slants, was grown for 24 h in a culture medium of distilled water (100 mL) containing yeast extract (0.3 g), KH_2PO_4 (0.5 g), and $Na_2HPO_4 \cdot 12H_2O$ (0.12 g). A sterile solution (100 mL) of this medium was inoculated with previous culture (10 mL), and, after 8 h of agitation on a rotatory shaker at 30 °C, **3** (50 mg, 0.185 mmol) in DMF (2 mL) was added and incubated for 46 h in the same conditions. Final pH (≈7) was brought to 3.5 by addition of 1 M HCl. Ten such experiments were combined, and, after adding CH_2Cl_2 (500 mL) with shaking, the mixture was filtered and the residue and the aqueous layer were extracted separately with CH_2Cl_2. The combined organic extracts (2 L) were washed with a saturated solution of $NaHCO_3$ and water and then dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue (510 mg), which was crystallized from acetone–petroleum ether, affording **4** (365 mg, 74%), mp 258–261 °C (lit.[3b] mp 261–263 °C).

3-Methoxyestra-1,3,5(10),6-tetraen-17-one (5). To a well-stirred solution of **4** (500 mg, 1.86 mmol) in methanol (100 mL), at ambient temperature, were added dropwise and simultaneously a 6.2 M aqueous solution of potassium hydroxide (2 mL, 12.4 mmol) and dimethyl sulfate (1 mL, 1.3 g, 10.3 mmol) under N_2 atmosphere, and the mixture was stirred for 10 min. After two more dropwise additions of potassium hydroxide solution (1 mL) and dimethyl sulfate (1 mL), the alkaline solution was stirred for 12 h. Finally, a new addition of the two reagents (1 mL each) was made, and the resulting mixture was heated under reflux for 1 h. Most of the solvent was distilled under reduced pressure, and the residue was diluted with water (250 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with water (250 mL) and dried over $MgSO_4$. Evaporation of solvent gave a solid (535 mg), which was crystallized from methanol to give pure **5**; 474 mg (90%); mp 121–123 °C (lit.[8] mp 118–120 °C); IR (KBr) 1740, 1605, 1570, 1495, 1260, 1050 cm^{-1}; UV λ_{max} (ϵ) 222 (29 200), 262 (7400), 302 (2500); ^{1}H NMR δ 7.16 (d, J = 7.9 Hz, 1 H, 1-CH), 6.73 (dd, J = 7.9 Hz, J = 2.7 Hz, 1 H, 2-CH), 6.66 (d, J = 2.7 Hz, 1 H, 4-CH), 6.51 (d, J = 11.8 Hz, 1 H, 6-CH), 6.05 (d, J = 11.8 Hz, 1 H, 7-CH), 3.80 (s, 3 H, 3-CH_3O), 0.91 (s, 3 H, 18-CH_3); MS m/z (relative intensity) 282 (M^+, 100), 226 (11), 225 (20), 197 (48), 184 (69), 171 (67), 158 (63).

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Registry No. **1**, 434-22-0; **2**, 734-32-7; **3**, 13209-45-5; **4**, 2208-12-0; **5**, 17253-36-0.

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(8) CIBA Ltd. Fr. Patent 1418540, 1975; *Chem. Abstr.* **1968**, *68*, 39953.

Acyl Anion Equivalents in the Synthesis of 2*H*-Pyran-2-ones: An Efficient Synthesis of Anibine†

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A number of 4-hydroxy-2*H*-pyran-2-ones and their methyl ethers have been isolated from natural sources.[1] Some of these, e.g. anibine (**1d**) and its analogues **1a** and **1b**, show interesting pharmacological properties.[1] Synthetic efforts toward construction of 2*H*-pyran-2-ones are

† Dedicated to Prof. N. S. Narasimhan on his 60th birthday.

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