with acetonitrile (200 mL). After evaporation of the acetonitrile, a residue was obtained which was converted to its hydrochloride salt in the same manner as described in general procedure. IR, NMR, and mass spectra were identical with those of intermediate **6a** produced in the aryne reaction. TLC of residue indicated only traces of **5a**.

Registry No. 3a, 1020-39-9; **3a'**, 6004-21-3; **3a''**, 70787-27-8; **3a'''**, 10286-85-8; **3b**, 2596-93-2; **3c**, 7465-92-1; **3d**, 77791-06-1; **3d'**, 77791-07-2; **3e**, 49747-46-8; **3f**, 77791-08-3; **3g**, 77791-09-4; **3h**, 10286-86-9; **3i**, 18931-78-7; **3j**, 77791-10-7; **5a**, 833-50-1; **5b**, 273-53-0; **5c**, 838-34-6; **5d**, 14016-00-3; **5e**, 835-71-2; **5f**, 14625-58-2; **5g**, 3164-18-9; **5h**, 77791-11-8; **5i**, 53012-61-6; **5j**, 77791-12-9; **6a**·HCl, 77791-13-0; **6b**·HCl, 77791-14-1; **6c**, 77791-15-2; **6d**·HCl, 77791-16-3; 2-chlorobenzenamine, 95-51-2; 3-chlorobenzenamine, 108-42-9; 2-bromobenzenamine, 615-36-1; 3-bromobenzamine, 591-19-5; 2-bromo-4-methylbenzenamine, 583-68-6; 2-chloro-4-methylbenzenamine, 615-65-6; 2-chloro-6-methylbenzenamine, 87-63-8; 2-chloro-4-methoxybenzenamine, 29242-84-0; benzoyl chloride, 98-88-4; formyl chloride, 2565-30-2; 4-methoxybenzoyl chloride, 100-07-2; 4-methylbenzoyl chloride, 874-60-2; 3-methylbenzoyl chloride, 1711-06-4; acetyl chloride, 75-36-5; 1-naphthalenecarbonyl chloride, 879-18-5.

Selenosteroids as Potential Estrogen-Receptor Scanning Agents[1,2]

Samy A. Sadek,[3a] Stanley M. Shaw,[3a] Wayne V. Kessler,[3a] and Gordon C. Wolf*[3a,b]

Department of Bionucleonics and the School of Health Sciences and the Department of Medicinal Chemistry and Pharmagognosy, Purdue University, West Lafayette, Indiana 47907

Received February 20, 1981

In an effort to produce effective breast tumor imaging agents, a series of selenium-labeled steroids have been synthesized and characterized. Starting with natural estrone, derivatives containing (nonradioactive) selenium at positions 3, 16, and 17 were obtained. Estrogen-receptor assays reveal 17α-[(phenylseleno)methyl]-17β-estradiol, **8c**, retains approximately 12% of the binding activity of 17β-estradiol.

Radiolabeled pharmaceuticals for use as nuclear scanning agents have a tremendous potential in diagnostic medicine. Current efforts are toward synthesis of more specific radiotracers that bind preferentially to appropriate receptor targets, i.e., adrenergic, progesterone, and estrogen receptors.[4] To date, most such agents employ radioactive iodine (either ^{125}I or ^{131}I) as the γ-emitting isotope. Such a choice has both advantages (ease of preparation, excellent scanning properties) and disadvantages (biological and chemical instability). We felt that appropriate radiotracers labeled with ^{75}Se offered some distinct attractions, i.e., satisfactory scanning qualities (witness the commercially utilized [^{75}Se]methionine for pancreatic imaging), ease of chemical synthesis, and, hopefully, much improved biological stability. To this end, we report our current synthetic results aimed at the preparation of various selenium-labeled (at present, nonradioactive) steroidal estrogens. Abbreviated biological assays confirm that such agents can be produced which retain a significant estrogen-receptor affinity.[5]

With few exceptions,[6] previous attempts at producing potential estrogen-receptor scanning agents have met with only limited success, primarily because specificity is lost as the radiolabel is attached to inappropriate positions on the steroid nucleus.[7] From previous studies, it would appear that substitution on the D ring (17α or 16) would hold the most promise for retaining receptor affinity; conversely, for purposes of receptor binding, the aromatic A ring tolerates substitution poorly; furthermore, the 3-phenolic hydroxyl moiety is imperative. 16α-Iodo-[6a] and -bromo-17β-estradiol[8] retain 100% and 127%, respectively, of the binding affinity of 17β-estradiol.

Scheme I illustrates our current synthetic approaches. Estrone methyl ether, **5a**, was initially chosen as the starting material due to its availability and to the chemical inertness of the methyl protecting group. However, attempts to remove this group and produce the (more desirable) phenolic alcohol as a final step in the synthetic route led to significant difficulty. Therefore, we ultimately came to employ the more easily removed tetrahydropyranyl ether, **5b**.

The 16,17-olefin, **3a**, was prepared from **5a** via the 17-toluenesulfonylhydrazone and *n*-butyllithium in 42% yield. Subsequent epoxidation with *m*-chloroperbenzoic acid provided an 80:20 mixture of the α and β 16,17-epoxides. The former was readily separable simply by fractional crystallization. Dimethylaluminum methylselenolate[9] gave 16β-(methylseleno)-17α-estradiol 3-methyl ether, **1**, in 54% yield. Though rigorous proof of the orientation of the D-ring substituents is not provided, the indicated structure is consistent with the expected trans ring opening of the α-epoxide, keeping in mind the steric requirements of the 17 angular methyl group. Too, only one product was evident by TLC and NMR analysis of the reaction mixture.

16α-(Phenylseleno)estrone, **2c**, was prepared from **5b** (as was the methyl derivative from **5a**), utilizing the lithium enolate and phenylselenyl chloride (diphenyl diselenide

(1) Presented in part at the 179th National Meeting of the American Chemical Society, Houston, TX, March 20–27, 1980.

(2) Financial support received from the Indiana Elks Research Fund, Grant 0209-63-1333, and the Purdue University Cancer Research Committee.

(3) (a) Department of Bionucleonics and the School of Health Sciences; (b) Department of Medicinal Chemistry and Pharmacognosy.

(4) (a) Eckelman, W. C.; Reba, R. C.; Gibson, R. E.; Rzeszotarski, W. J.; Vieras, F.; Mazaitis, J. K.; Francis, B. *J. Nucl. Med.* **1979**, *20*, 350. (b) Arunchalam, T.; Longcope, C.; Caspi, E. *J. Biol. Chem.* **1979**, *254*, 5900. (c) Mazaitis, J. K.; Gibson, R. E.; Komai, T.; Eckelman, W. C.; Francis, B.; Reba, R. C. *J. Nucl. Med.* **1980**, *21*, 142.

(5) Anderson, J.; Clark, J. H.; Peck, E. J., Jr. *Biochem. J.* **1972**, *126*, 561. Estrogen-receptor assays have been graciously performed by Dr. J. Anderson of the Purdue Biological Sciences Department; we express our gratitude.

(6) (a) Hochberg, R. B. *Science* **1979**, *205*, 1138. (b) Hochberg, R. B.; Rosner, W. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 328. (c) Goswami, R.; Harsy, S. G.; Herman, D. F.; Katzenellenbogen, J. *J. Med. Chem.* **1980**, *23*, 1002.

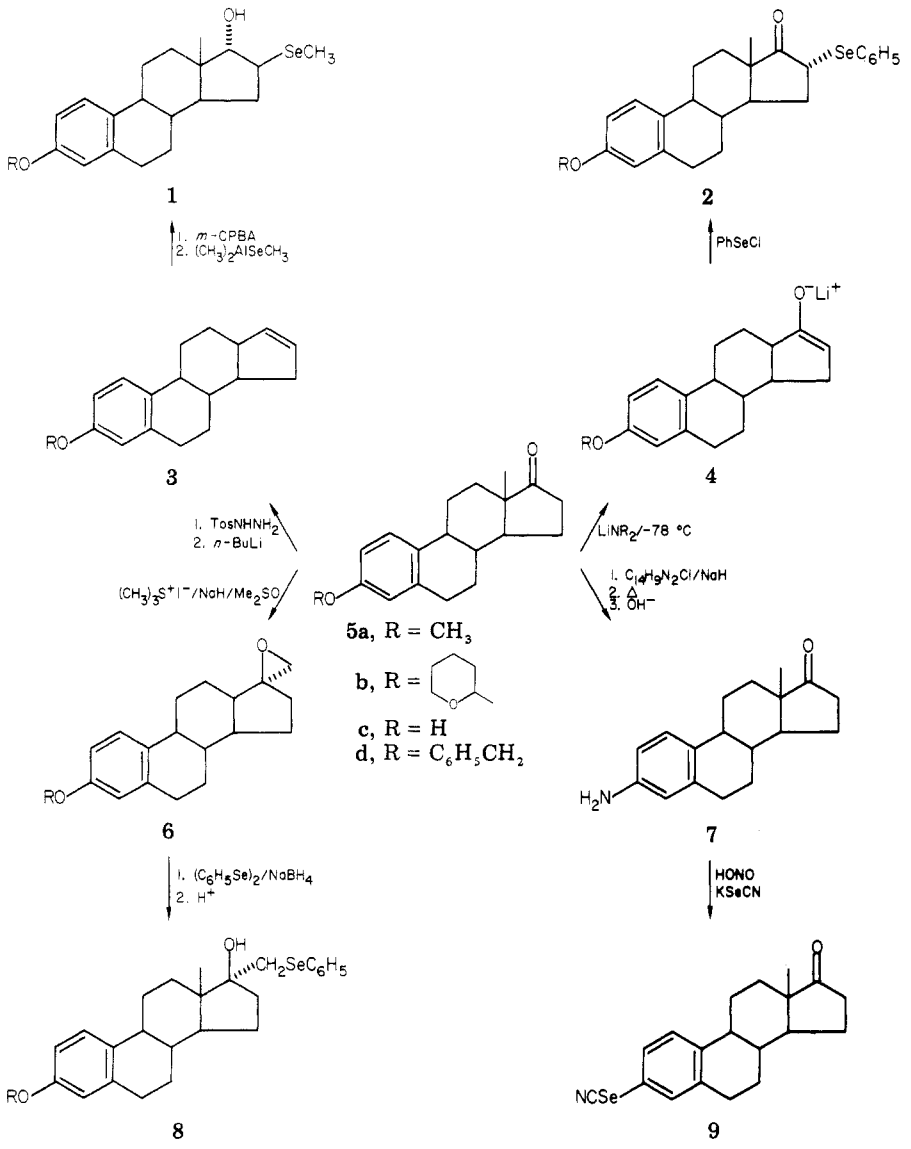
(7) Komai, T.; Eckelman, W. C.; Johnsonbaugh, R. E.; Mazaitis, A.; Kubota, H.; Reba, R. C. *J. Nucl. Med.* **1977**, *18*, 360.

(8) Heiman, D. F.; Senderoff, S. G.; Katzenellenbogen, J.; Neeley, R. J. *J. Med. Chem.* **1980**, *23*, 994.

(9) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2735.

0022-3263/81/1946-3259$01.25/0

Scheme I



worked less well). Two products were obtained and were identified as the 16α and 16β derivatives by their NMR spectra. Thus, similar epimers of androst-5-en-17-one have recently been obtained and their NMR spectra published.[10] Spectral comparison, as well as steric considerations, reveal our major product to be of the 16α orientation, **2c**. 17α-Substitution was approached through use of dimethylsulfonium methylide to produce the 17-spirosteroid, **6**;[11] opening of the epoxide ring was easily accomplished with sodium phenyl selenide. Our initial sequence started with the 3-benzyl ether derivative, **6d**, but again we found it difficult to remove the benzyl group and therefore employed the tetrahydropyranyl moiety. Mild acid hydrolysis then provided **8c** as a readily crystallizable solid. However, it was necessary to utilize *p*-toluenesulfonic acid rather than dilute HCl in order to obviate HCl incorporation in the crystalline product.

A final synthetic objective was to prepare a 3-substituted selenium derivative, rationalizing that, because of the same grouping in the periodic chart, selenium and oxygen may have similar receptor binder affinities. Thus, 3-aminoestra-1,3,5(10)-trien-17-one, **7**, was prepared according to Morrow,[12] using commercially available 4-chloro-2-phenyl-1,3-quinazoline with estrone, **5c**, and sodium hydride. Subsequent pyrolytic rearrangement and hydrolysis led to **7** in 34% yield. Diazotization with nitrous acid followed by reaction of the 3-diazoestrone with potassium selenocyanate then gave a moderate yield of crystalline 3-(selenocyanato)estra-1,3,5(10)-trien-17-one, **9**. Subsequent attempts at reduction to the free selenol (with or without reduction of the 17-ketone) have failed to provide a pure material, presumably secondary to concurrent production of the diselenide.

Discussion

We have shown the feasibility of synthesizing various 3, 16, and 17 selenium-substituted estrogenic steroids employing relatively simple chemical means. Biological activity (receptor binding) would be expected to be minimal without a free 3-hydroxyl group. Thus, while our initial work with **5a** and **5d** provided access to selenium-labeled products, our present efforts utilize **5b**.

Initial receptor binding assays have been carried out with **1**, **2a**, **8c**, **8d**, and **9**.[5] As might be predicted, **8c** bound significantly to estrogen receptors, whereas the remaining agents, with the 3-OH group protected (or absent), did not,

(10) Konopelski, J. P.; Djerassi, C. *J. Med. Chem.* **1980**, *23*, 722.
(11) Lam, H. P.; Begleiter, A.; Goldenberg, G. J.; Won, C. M. *J. Med. Chem.* **1979**, *22*, 200.
(12) Morrow, D. F.; Hofer, R. M. *J. Med. Chem.* **1966**, *9*, 249.

and therefore reaffirms the importance of this entity. It is also noted, however, that only 8c possesses both the 17β-OH moiety as well as the free 3-OH group.

Future efforts will be directed toward preparation of other 16- and 17-substituted estrogenic steroids containing the 3-hydroxyl moiety. Incorporation of selenium-75 into 8c is also underway, utilizing radioactive and commercially available phenylselenol.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Melting points (Pyrex capillary) are uncorrected. ^1H NMR spectra were determined on a Varian EM-360 or Varian FT-80 spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the following order: multiplicity, number of protons (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz. Mass spectra were obtained with Du Pont 21-492 B and CEC 110 double-focusing mass spectrometers. Elemental analyses were performed by the Microanalytical Laboratory operated by Doctor C. S. Yeh, Department of Chemistry, Purdue University, and by Galbraith Laboratories, Knoxville, TN.

3-Methoxy-1,3,5(10)-16-estratetraene (3). Estrone 3-methyl ether (6.85 g, 0.03 mol) and *p*-toluenesulfonyl hydrazide (5.59 g, 0.03 mol) were combined in 250 mL of THF along with 5 drops of concentrated HCl. The solution was refluxed for 14 h and stirred at room temperature for 24 h. A white powder (8.78 g; mp 194–196 °C; 74%) (lit.[13] mp 198 °C) was isolated after the solvent was evaporated and the solid recrystallized from 95% ETOH.

This material (7.92 g, 0.02 mol) was dissolved in 400 mL of diethyl ether under nitrogen. *n*-Butyllithium (18 mL of 2.42 M in hexane (0.044 M)) was added with stirring over 15 min. After 1 h, 200 mL of H_2O saturated with NH_4Cl was added carefully and the layers were separated. The ether layer was washed with water, dried over $MgSO_4$, and filtered, and the solvent evaporated to leave a pale, yellow oil which was chromatographed over 800 g of 60-mesh Florisil, using 1000 mL of benzene in hexane. Fifty-milliliter fractions were collected and the solvent was evaporated. Fractions 3–6 were combined, and the solid was recrystallized from 2-propanol to provide 2.25 g (42%) of white needles, mp 69–70 °C (lit.[14] mp 71–72 °C).

16β-(Methylseleno)-17α-estradiol 3-Methyl Ether (1). The above 16,17-olefin (0.67 g, 2.5 mmol) and *m*-chloroperbenzoic acid (0.53 g of 85% reagent, Aldrich; 2.6 mmol) were combined in 100 mL of dry CH_2Cl_2 at 0 °C and allowed to warm to room temperature over 1 h with stirring. A saturated solution of $NaHCO_3$ in 100 mL of H_2O was added, and the CH_2Cl_2 layer was separated, dried over $MgSO_4$, and filtered. Thin-layer chromatography (silica gel with solvent of 1% MeOH in benzene) revealed two components (no starting material) in the ratio of approximately 80:20. Evaporation of the solvent left a white powder which was readily recrystallized from MeOH to give 240 mg of broad needles, mp 115–118 °C (lit.[14] mp 117–119 °C), 34%.

A solution of dimethylaluminum methylselenolate was prepared by adding 25.2 mL (0.05 mol) of 17% trimethylaluminum in toluene (Ethyl Corp.) to 4.1 g (0.52 mol) of powdered selenium (Alpha Inorganics) under N_2 (caution!). A mild exothermic reaction ensued, and the solution was stirred at ambient temperature for 1 h. The pale, yellow solution (1 mL, 2.0 mmol) was added to the epoxide (220 mg, 0.77 mmol) in 10 mL of CH_2Cl_2 at 0 °C. This solution was allowed to stir while warming to room temperature over 1 h. Careful addition of 20 mL of H_2O containing 1 g of Na_2SO_4 was followed by separation of layers, drying over $MgSO_4$, filtering, and solvent evaporation. A pale yellow oil was obtained and dissolved in 5 mL of MeOH and refrigerated for 3 days, whereupon 160 mg of long, flat needles was collected: 54%; mp 91–92 °C; NMR δ 0.92 (s, 3 H, $C_{18}H_3$), 2.13 (s, 3 H, $SeCH_3$), 3.84 (s, 3 H, OCH_3), 6.75–7.45 (m, 3 H, Ar H); mass spectrum, *m/e* 380 (M^+). Anal. Calcd for $C_{20}H_{27}O_2Se$: C, 63.31; H, 7.44; Se, 20.81. Found: C, 63.16; H, 7.30; Se, 20.71.

16α-(Phenylseleno)estrone 3-Methyl Ether (2a). *N*-Isopropylcyclohexylamine (3 mmol, 0.49 mL) was added to 10 mL of THF at −78 °C, under nitrogen, followed by 1.88 mL (3 mmol) of 1.6 M *n*-BuLi in hexane. A solution of estrone 3-methyl ether (711 mg, 2.5 mmol) in THF was added dropwise and the solution was stirred for 15 min. Phenylselenyl chloride (0.574 g, 3 mmol) in THF (3 mL) was added to the reaction mixture rapidly. The cold reaction mixture was poured into 25 mL of 0.5 N HCl and 40 mL of ether, and the organic layer was washed with water and dried over anhydrous $MgSO_4$. Ether was evaporated at room temperature. The residue obtained was dissolved in methyl alcohol and a few drops of THF and left in a refrigerator for 2 days. A solid was obtained and recrystallization from 95% ETOH provided 400 mg of white crystals (36%): mp 130–131 °C; NMR δ 0.92 (s, 3 H, $C_{18}H_3$), 3.8 (s, 3 H, methoxy H), 6.65–7.85 (m, unresolved, 8 H, Ar H); mass spectrum, *m/e* 441 (M^+). Anal. Calcd for $C_{25}H_{28}O_2Se$: C, 68.33; H, 6.42. Found: C, 68.56; H, 6.44.

In a similar sequence, **2b** (mp 151–152 °C) was obtained and, after hydrolysis, **2c** (mp 185–186 °C).

17α-[(Phenylseleno)methyl]-17β-estradiol (8). Estrone 3-tetrahydropyranyl ether (10.63 g, 0.03 mol; prepared from 10.0 g of estrone and 30 mL of dihydropyran) was added (N_2) in portions to a cooled (ice) solution of NaH (50% in mineral oil, 4.32 g, 0.09 mol), Me_2SO (75 mL), THF (100 mL), and trimethylsulfonium iodide (18.36 g, 0.109 mol) which had previously been heated to 75 °C for 30 min. After 1 h at ambient temperatures, the solution was poured into ice–water and extracted with two 100-mL portions of ether. The organic extracts were combined, dried over $MgSO_4$, and filtered, and the solvent was evaporated. The resulting solid was recrystallized from benzene/hexane to give 8.51 g (79%) of **6b**: mp 97–98 °C; NMR δ 0.92 (s, 3 H, $C_{18}H_3$), 2.85 (AB q, 2 H, oxirane CH_2), 6.83–7.34 (m, 3 H, Ar H); mass spectrum, *m/e* 369 (M^+). Anal. Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.40; H, 8.67%.

The 17-spirosteroid (1.79 g, 5.0 mmol) in 20 mL of THF was added to a solution of diphenyl diselenide (0.94 g, 3.0 mmol) and $NaBH_4$ (0.23 g, 6.1 mmol) in 20 mL of ETOH. After being heated to gentle reflux for 30 min, the solution was cooled overnight and then washed with 100 mL of 10% NaOH followed by 100 mL of H_2O. Drying and solvent evaporation left a yellow oil which solidified on standing. This solid was recrystallized from absolute ETOH to give white needles, 1.79 g, 70% (**8b**, mp 129–130 °C). One gram of this solid was then dissolved in 50 mL of 95% ETOH and 10 mL of H_2O. To this was added 0.15 g of *p*-toluenesulfonic acid. After 4 h at 40 °C, 200 mL of H_2O was added and the solution extracted with two 50-mL portions of ether. The latter were combined and dried ($MgSO_4$), and the solvent was evaporated. The resulting solid was recrystallized from benzene to give 0.83 g of **8c**: mp 103–104 °C; NMR δ 0.96 (s, 3 H, $C_{18}H_3$), 3.27 (AB q, 2 H, $C_{19}H_2$), 6.55–7.64 (m, 8 H, Ar H); mass spectrum, *m/e* 443 (M^+). Anal. Calcd for $C_{25}H_{30}O_2Se$: C, 68.02; H, 6.85. Found: C, 68.03; H, 6.83%.

The benzyl derivatives were likewise obtained: **6d**, mp 158–160 °C (lit.[11] mp 155–157 °C); **8d**, mp 105–106. Anal. Calcd for **8d**, $C_{32}H_{36}O_2Se$: C, 7.94; H, 6.62. Found: C, 7.93; H, 6.69.

3-(Selenocyanato)estra-1,3,5(10)-trien-17-one (9). 3-Aminoestra-1,3,5(10)-trien-17-one[12] (538 mg, 2.0 mmol) was dissolved in a solution containing 50 mL of ETOH and 10 mL of 10% aqueous HCl and coooled to 0 °C. A solution of $NaNO_2$ (414 mg, 6.0 mmol) in 20 mL of H_2O was added rapidly to give a dark, brown solution. KSeCN (804 mg, 5.6 mmol) in 50 mL of H_2O was cooled to 0 °C and added slowly to the like-cooled diazonium solution after the latter had been made neutral to Congo Red paper by the addition of solid NaOAc. After warming to room temperature for 2 h, the solution was extracted twice with 50-mL portions of $CHCl_3$. These were combined, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The red-brown gum was then chromatographed over 400 g of 60-mesh Florisil, using as the eluent: 200 mL of C_6H_6, 200 mL of 1% MeOH/C_6H_6, and 200 mL of 2% MeOH/C_6H_6. Fractions containing 25 mL each were collected and the solvent was allowed to evaporate at room temperature. A pale yellow crystalline solid was found in fractions 3–5 and was combined and recrystallized from benzene/hexane

(13) Caglioti, L.; Magi, M. *Tetrahedron* **1963**, *19*, 1127.
(14) Mueller, G. P.; Johns, W. F. *J. Org. Chem.* **1961**, *26*, 2403.

Table I. Relative Binding Affinities

compd	relative binding affinity[a]
17β-estradiol	100
17α-[(phenylseleno)methyl]-17β-estradiol (8)	11.8
16β-(methylseleno)-17α-estradiol 3-methyl ether (1)	<0.1
16α-(phenylseleno)estrone 3-methyl ether (2)	<0.1
3-(selenocyanato)estrone (9)	<0.1

[a] Calculated at $B/B_0 = 50\%$.[15]

to give 150 mg (21%) of **9**: mp 164–165 °C; NMR δ 0.91 (s, 3 H, $C_{18}H_3$), 7.25–7.37 (m, 3 H, Ar H); mass spectrum, *m/e* 360 (M^+). Anal. Calcd for $C_{19}H_{21}NOSe$: C, 63.67; H, 5.91. Found: C, 63.65; H, 6.00.

Binding Studies. The binding of the selenosteroids was analyzed by the [17β-^{3}H]estradiol exchange assay as described by Anderson.[5] Immature (21–25 day) female Sprague–Dawley rats were injected subcutaneously with 5 mg of 17β-estradiol in 0.5 mL of 0.9% NaCl. The animals were killed 45 min to 1 h after injection and the uterine nuclear fraction in TE buffer (0.01 M Tris-HCl, pH 7.4, containing 1.5 mM EDTA) was incubated at 37 °C for 30 min with 2×10^{-8} M [17β-^{3}H]estradiol. Following incubation, the nuclear fractions were washed with TE buffer followed by centrifugation at 800*g* for 10 min. The washed pellet was extracted with ethanol. The extract was added to 10 mL of scintillation fluid [99.5% toluene, 0.45% 2,5-diphenyloxazole, 0.05% 1,4-bis(5-phenyloxazol-2-yl)benzene]. The amount of [17β-^{3}H]estradiol bound was determined with an internal sample liquid scintillation counting system. For competitive-inhibition experiments, various concentrations (10^{-10}–10^{-5} M) of nonradioactive 17β-estradiol or of selenosteroid were added to the reaction mixture together with [17β-^{3}H]estradiol and incubated as described. The results are summarized in Table I.

Registry No. **1a**, 77862-28-3; **2a**, 77942-76-8; **2b**, 77862-29-4; **2c**, 77862-30-7; **3a**, 28336-31-4; **5a**, 1624-62-0; **5a** toluenesulfonylhydrazone, 32164-54-8; **5b**, 7103-48-2; **6b**, 77862-31-8; **6d**, 68687-35-4; **7**, 18119-98-7; **8b**, 77862-32-9; **8c**, 77862-33-0; **8d**, 77882-19-0; **9**, 77862-34-1; 17β-estradiol, 50-28-2; **3a** α-epoxide, 28336-32-5; **3a** β-epoxide, 28344-30-1.

(15) Rodhard, D. *Adv. Exptl. Med. Biol.* **1973**, *36*, 298–326.

Facile, High-Yield Synthesis of Spiro C-17 Steroidal Oxetan-3′-ones

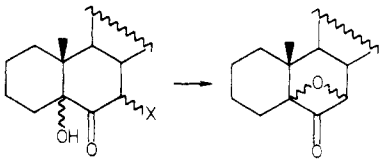
Michel Pons and S. Stoney Simons, Jr.*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20205

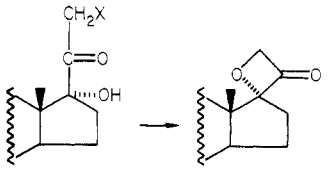
Received March 2, 1981

The facile, high-yield conversion of C-17 α-keto mesylates of glucocorticoids to spiro C-17 oxetan-3′-ones is described. This reaction, involving treatment with strong base (KOH, NaOMe, or KO-*t*-Bu) in EtOH or THF, represents a major improvement for the preparation of these steroid derivatives.

Oxetan-3-ones are four-membered-ring compounds of which only a few examples are known.[1,2] For some reason, steroidal oxetan-3′-ones are readily isolated.[3-9] While there are several methods of preparing oxetan-3-ones (by oxidation,[10-13] by acid-catalyzed decomposition of diazo ketones,[2,14] by photochemical [$_\pi$2 + $_\pi$2] cycloaddition,[15] by epoxidation of allenes,[16] and by intramolecular displacement reactions[3-9]), only intramolecular displacements have been used to prepare steroidal oxetan-3′-ones. These displacements work well for the selective preparation of the α or β 5,7-oxetan-3′-ones (**1** → **2**).[7-9] In contrast, the synthesis of C-17 oxetan-3′-ones (**3** → **4**) requires much more forcing reaction conditions (16 h/80 °C to 24 h/110 °C vs. 7 min/room temperature to 2 h/100 °C for **1** → **2**) and proceeds in poor yields.[3-6] Previous attempts to increase the rate of reaction of **3** → **4** have been unsuccessful.[6] Here we report apparently general conditions which overcome these problems and rapidly provide the C-17 oxetan-3′-ones (**4**) in high yield.



1 **2**



3 **4**

Results and Discussion

During our recent investigation of α-keto mesylates such as **3** (X = OSO_2CH_3),[17] we noted that no reaction of the

(1) Donnelly, J. A.; Hoey, J. G.; O'Donnell, R. *J. Chem. Soc., Perkin Trans 1*, **1974**, 1218–1220.
(2) Ducruix, A.; Pascard, C.; David, S.; Fischer, J.-C. *J. Chem. Soc., Perkin Trans 2* **1976**, 1678–1682.
(3) Herz, J. E.; Fried, J.; Grabowich, P.; Sabo, E. F. *J. Am. Chem. Soc.* **1956**, *78*, 4812–4814.
(4) Hirschmann, R.; Bailey, G. A.; Poos, G. I.; Walker, R.; Chemerda, J. M. *J. Am. Chem. Soc.* **1956**, *78*, 4814.
(5) British Patent 869,564, 1962; *Chem. Abstr.* **1962**, *56*, 2490*d*.
(6) Heller, M.; Lenhard, R. H.; Bernstein, S. *Steroids* **1965**, *5*, 615–635.
(7) Rowland, A. T.; Bennett, P. J.; Shoupe, T. S. *J. Org. Chem.* **1968**, *33*, 2426–2436.
(8) Hanna, R.; Maalouf, G.; Muckensturm, B.; Cherry, A. *Tetrahedron* **1973**, *29*, 2297–2303.
(9) Rowland, A. T.; Drawbaugh, R. S.; Dalton, J. R., *J. Org. Chem.* **1977**, *42*, 487–490.
(10) Hoey, C. B.; Dean, D. O.; Lester, C. T. *J. Am. Chem. Soc.* **1955**, *77*, 391–393.
(11) Murr, B. L.; Hoey, G. B.; Lester, C. T. *J. Am. Chem. Soc.* **1955**, *77*, 4430–4431.
(12) Harper, J. L.; Lester, C. T. *J. Org. Chem.* **1961**, *26*, 1294–1295.
(13) Wojtowicz, J. A.; Polak, R. J. *J. Org. Chem.* **1973**, *38*, 2061–2066.
(14) Marshall, J. R.; Walker, J. *J. Chem. Soc.* **1952**, 467–475.
(15) Schroeter, S.; Orlando, C. M., Jr. *J. Org. Chem.* **1969**, *34*, 1181–1187.
(16) Crandall, J. K.; Machleder, W. H.; Thomas, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 7346–7347.
(17) Simons, S. S. Jr.; Pons, M.; Johnson, D. F. *J. Org. Chem.* **1980**, *45*, 3084–3088.