the multiplet at δ 2.4, gave δ 5.93 (d, J = 10.4 Hz), and sharpened the dd at δ 6.07; mass spectrum, m/e 234 (M^+). Anal. Calcd for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02; S, 13.68. Found: C, 66.46; H, 6.08; S, 13.86.

2-(*p*-Toluenesulfonyl)indene (24a): IR ($CHCl_3$) 1303, 1147 cm^{-1}; ^1H NMR (60 MHz) 7.87 (d, J = 8 Hz, 2 H), 7.65 (t, J = 2 Hz, 1 H), 7.55–7.20 (m, 6 H), 3.62 (d, J = 2 Hz, 2 H), 2.40 (s, 3 H); mass spectrum, m/e 270 (M^+). Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 71.05; H, 5.44; S, 11.82.

2-(Benzenesulfonyl)indene (24b): IR ($CHCl_3$) 1308, 1151 cm^{-1}; ^1H NMR as reported in the literature;[22] mass spectrum, m/e 256 (M^+).

(*E*)-3-(Benzenesulfonyl)-2-propenyl Phenyl Ether (25): IR (Nujol) 1640, 1308, 1147 cm^{-1}; ^1H NMR (200 MHz) 7.89 (dt, J = 6.6, 1.4 Hz, 2 H), 7.70–7.50 (m, 3 H), 7.30–7.22 (m, 2 H), 7.12 (dt, J = 15.0, 3.3 Hz, 1 H), 6.97 (t, J = 7.5 Hz, 1 H), 6.86 (dd, J = 7.8, 1.2 Hz, 2 H), 6.76 (dt, J = 15.0, 2.2 Hz, 1 H), 4.72 (dd, J = 3.3, 2.2 Hz, 2 H); double irradiation at δ 4.7 gave δ 7.12 (d, J = 15.0 Hz), 6.76 (d, J = 15.0 Hz); mass spectrum, m/e 274 (M^+). Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.66;, H, 5.15; S, 11.70. Found: C, 65.69; H, 5.07; S, 11.49.

(*E*)-1-Cyano-2-(*p*-toluenesulfonyl)ethene (26). The product had IR and ^1H NMR spectra as reported in the literature;[20] mass spectrum, m/e 207 (M^+).

(*Z*)- and (*E*)-5-(*p*-Toluenesulfonyl)-5-decenes (27a,b). Oxidation of **14a** and **14b** (1:4.5, obtained by the thermal addition of **1a** to 5-decene) in the usual manner gave a mixture of sulfones **27a** and **27b**: ^1H NMR (200 MHz) showed signals at δ 6.86 (t, J = 7.6 Hz, E sulfone) and 5.96 (tt, J = 7.5, 1.1 Hz, Z sulfone) in a ratio of 4.3:1; GC/MS analysis showed both components with m/e 294 (M^+).

Oxidation of pure **14b** gave only the E sulfone **27b**: IR (film) 1640, 1301, 1138, cm^{-1}; ^1H NMR (60 MHz) 7.65 (d, J = 8 Hz, 2 H), 7.20 (d, J = 8 Hz, 2 H), 6.86 (t, J = 7.6 Hz, 1 H), 2.40 (s, 3 H), 2.40–2.00 (m, 4 H), 1.70–0.70 (complex, 14 H); high-resolution mass spectrum calcd for $C_{17}H_{26}O_2S$ m/e 294.1655, found m/e 294.1644.

Acknowledgment. We thank Dr. D. G. Garratt for a gift of (*E*)- and (*Z*)-1-phenylpropene. We are also grateful to Professor J. L. Kice for informing us of his work on photoinitiated selenosulfonation prior to its publication.

Registry No. 1a, 68819-94-3; **1b**, 60805-71-2; **3**, 76649-90-6; **4a**, 76649-84-8; **4b**, 76649-85-9; **5a**, 76649-86-0; **5b**, 76649-87-1; **5c**, 76649-88-2; **5d**, 76649-89-3; **6a**, 77825-67-3; **6b**, 77825-68-4; **10**, 77825-69-5; **11a**, 77825-70-8; **11b**, 77825-71-9; **12**, 76649-92-8; **13**, 77825-72-0; **14a**, 77825-73-1; **14b**, 77882-25-8; **19**, 67963-03-5; **20a**, 77825-74-2; **20b**, 16212-08-1; **21a**, 77825-75-3; **21b**, 77825-76-4; **21c**, 77825-77-5; **21d**, 77825-78-6; **22a**, 77825-79-7; **22b**, 77825-80-0; **23**, 77825-81-1; **24a**, 77825-82-2; **24b**, 26189-65-1; **25**, 77825-83-3; **26**, 19542-67-7; **27a**, 77825-84-4; **27b**, 77825-85-5; boron trifluoride, 7637-07-2; cyclohexene, 110-83-8; styrene, 100-42-5; methyl 10-undecenoate, 111-81-9; (*E*)-1-phenylpropene, 873-66-5; (*Z*)-1-phenylpropene, 766-90-5; 1,3-cyclohexadiene, 592-57-4; indene, 95-13-6; allyl phenyl ether, 1746-13-0; acrylonitrile, 107-13-1; (*E*)-5-decene, 7433-56-9; (*Z*)-5-decene, 7433-78-5.

Investigation of the Synthesis of Benzoxazole via Aryne Reaction[1a]

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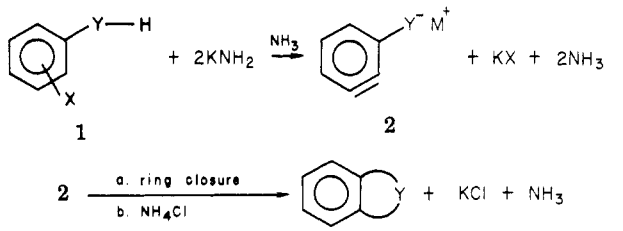
Received April 8, 1981

The reaction of *o*- and *m*-halobenzamides under aryne-forming conditions yielded the corresponding *o*-hydroxyphenyl amidines instead of the expected benzoxazole derivatives. The amidines, however, were converted to the corresponding benzoxazole either by sublimation or acidic hydrolysis. Evidence is presented that benzoxazoles are initially formed in these reactions but are readily aminated to the corresponding hydroxyphenyl amidines under the highly basic reaction conditions used in these aryne-forming reactions.

Bunnett[2,3] and Huisgen[4-7] have shown that aryne intermediates, **2**, which possess a strong nucleophile located suitably in a side chain undergo intramolecular nucleophilic addition to yield the corresponding ring-closure products. Arynes, **2**, are prepared by treating either ortho- or meta-substituted haloaromatics with a strong base, generally potassium amide in liquid ammonia or phenyllithium in ether. Several heterocyclic systems,[8] such as benzoxazoles, benzothiazoles, indoles, phenothiazine, etc., have been prepared in this manner, generally in good to excellent yields.

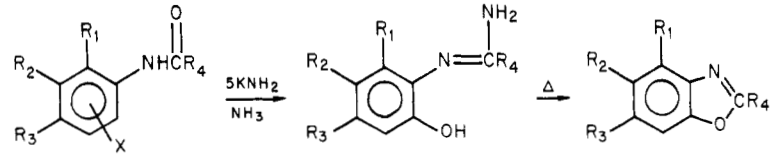


Heterocyclic ring systems which contain a C=N bond are susceptible to covalent solvation by nucleophilic solvents.[9] Of particular interest to us was the report[3] that 2-phenylbenzoxazole was prepared in 70% yield from the aryne reaction of 2-chlorobenzanilide and potassium amide in liquid ammonia. Many of these solvated heterocyclics undergo ring opening in the presence of strong bases; the

(1) (a) Supported in part by Grant N-118 of the Robert A. Welch Foundation, Houston, TX. (b) Robert A. Welch postdoctoral fellow. (c) Robert A. Welch predoctoral fellow.
(2) B. F. Hrutfiord and J. F. Bunnett, *J. Am. Chem. Soc.*, 80, 2021 (1958).
(3) B. F. Hrutfiord and J. F. Bunnett, *J. Am. Chem. Soc.* 83, 1691 (1961).
(4) R. Huisgen and H. Koenig, *Angew, Chem.*, 69, 268 (1957).
(5) R. Huisgen and H. Koenig, *Chem. Ber.*, 92, 203, 429 (1959).
(6) R. Huisgen, H, Koenig, and N. Bleeker, *Chem. Ber.*, 92, 424 (1959).
(7) R. Huisgen, H. Koenig, and A. R. Lepley, *Chem. Ber.*, 93, 1496 (1960).
(8) For a comprehensive listing see R. W. Hoffman, "Dehydrobenzene and Cycloalkynes", Academic Press, New York, 1969, pp 152–162.
(9) For a review on covalent hydration, see A. Albert, *Angew. Chem., Int. Ed. Engl.* 6, 919 (1967).

0022-3263/81/1946-3256$01.25/0

Table I. Preparation of (o-Hydroxyphenyl)benzamidines 6 and Benzoxazoles 5



3 6 5

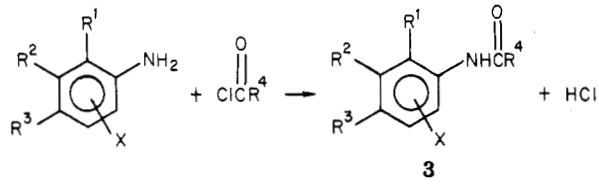
halo amide	R_1	R_2	R_3	R_4	X	mp, °C 3[a,b]	mp, °C 6	mp, °C 5	overall % yield of 5 from 3
3a	H	H	H	C_6H_5	o-Cl	101-102[c]	213-216[k]	102-103[l]	85
3a′					m-Cl	120-122[d]			74
3a″					o-Br	112-114[e]			78
3a‴					m-Br	135-136[f]			60
3b	H	H	H	H	o-Cl	76-78[g]	250-253[k]	28-30[m]	85
3c	H	H	H	p-$CH_3OC_6H_4$	o-Cl	140-141	235-250[h]	100-103[n]	75
3d	H	H	CH_3	C_6H_5	o-Cl	141-143[h]	163-170[k]	90-92[o]	68
3d′					o-Br	147-148[i]			70
3e	H	H	H	p-CH_3-C_6H_4	o-Cl	90-91	p	113-115[q]	65
3f	H	H	H	m-$CH_3C_6H_4$	o-Cl	105-106	p	81-82[r]	80
3g	H	H	H	α-$C_{10}H_7$	o-Cl	154-156[j]	p	104-105[s]	50
3h	CH_3	H	H	C_6H_5	o-Cl	144-145	p	92-93[t]	85
3i	H	H	CH_3	CH_3	o-Cl	133-135	p	117-118[u]	67
3j	H	H	OCH_3	C_6H_5	o-Cl	107-108	p	65-66[v]	

[a] Satisfactory analytical data (±0.4%) for C, H, and N were obtained for newly reported amide compounds. [b] Melting points for compounds recrystallized from 2-propanol/water. [c] Lit.[11] mp 99 °C. [d] Lit.[11] mp 118-120 °C. [e] Lit.[12] mp 116 °C. [f] Lit.[13] mp 135-136 °C. [g] Lit.[14] mp 77 °C. [h] Lit.[15] mp 137 °C. [i] Lit.[16] mp 147-148 °C. [j] Lit.[17] mp 150-151 °C. [k] Satisfactory elemental analysis was obtained for hydrochloride salt. [l] Lit.[18] mp 103 °C. [m] Lit.[19] mp 31 °C. [n] Lit.[20] mp 101 °C. [o] Lit.[21] mp 92-95 °C. [p] Too unstable for satisfactory melting point or elemental analysis. [q] Lit.[22] mp 113-115 °C. [r] Lit.[22] mp 115.5-116 °C. [s] Lit.[22] mp 104-105 °C. [t] Lit.[23] mp 92-93 °C. [u] Lit.[24] mp 117-118 °C. [v] Lit.[25] mp 65-66 °C.

Dimroth rearrangement[10] is one such example. In the original procedure described by Bunnett,[3] 2-phenylbenzoxazole was isolated by sublimation of an unidentified ethanol-soluble solid. Possibly this precursor is the o-hydroxyphenyl benzamidine formed by attack of amide ion on benzoxazole. We have now examined the preparation of several benzoxazoles by the aryne reaction and confirmed the presence of amidines, 6, in the reaction mixture.

Results and Discussion

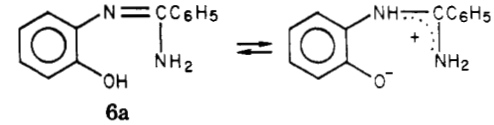
A series of halobenzamides, 3, was prepared by the Schotten–Baumann reaction. The percentage yields and certain physical properties of these amides are listed in Table I.



3

The aryne reaction of o-chlorobenzamide, **3a**, with potassium amide was repeated according to the procedure of Bunnett and the solid material, previously reported, was obtained. TLC showed this material to be composed of only 10% of the desired 2-phenylbenzoxazole, **5a**, and 90% of a polar material, **6a**.

Substance **6a** was fully characterized in the following way. The mass spectrum of **6a** revealed a parent ion at m/e 212, a fairly intense P − 17 peak at m/e 195 corresponding to loss of ammonia, and a base peak at m/e 109 representing, possibly, the o-aminophenol fragment ion. The IR spectrum (KBr) of **6a** showed a strong, very broad absorption band between 3100 and 2700 cm^{-1}, which is indicative of an ammonium salt. The ^1H NMR spectrum of **6a** showed three signals at δ 6.9 (9 H, m), 5.1 (2 H, m), and 8.2 (1 H); the latter two signals disappeared in the presence of D_2O. Further, **6a** was soluble in both 10% hydrochloric acid and 10% sodium hydroxide but not in 5% sodium bicarbonate, indicating the presence of a phenolic group and a basic group in **6a**. These data are



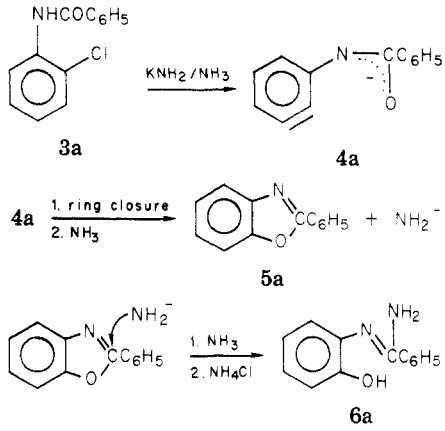
6a

consistent with **6a** being N-(o-hydroxyphenol)benzamidine which may also exist as an inner salt. Elemental analysis of the hydrochloride salt of **6a**, precipitated from cold, concentrated hydrochloric acid solution, was consistent with the assigned structure.

Intermediate **6a** was converted to 2-phenylbenzoxazole, **5a**, either by sublimation or hydrolysis in 10% (w/w)

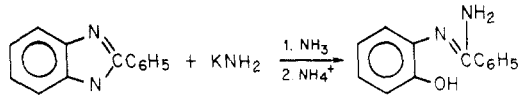
(10) For a general discussion, see D. J. Brown, "Mechanisms of Molecular Migrations", Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, 1968, pp 209–245.
(11) R. von Walther and A. Graesmann, *J. Prakt. Chem.* **78**, 486 (1908).
(12) F. D. Chattanny and J. M. Wadmore, *J. Chem. Soc.*, **81**, 986 (1902).
(13) F. B. Dains and R. M. Harger, *J. Am. Chem. Soc.*, **40**, 562 (1918).
(14) F. D. Chattanny and K. J. P. Orton, *Chem. Ber.*, **33**, 2396 (1900).
(15) S. Jadhaw, *J. Indian Chem. Soc.*, **15**, 649 (1938).
(16) J. Pinnow, *Chem. Ber.*, **24**, 4170 (1891).
(17) G. Choriav, *Chim. Fr.*, **12**, 105, 109 (1945).
(18) H. Hubner and H. Morse, *Chem. Ber.*, **7**, 1319 (1874).
(19) A. Ladenburg, *Chem. Ber.*, **10**, 1124 (1877).
(20) Z. H. Skranp, *Justus Liebigs Ann. Chem.*, **419**, 83 (1919).
(21) F. Henrich, *Chem. Ber.*, **54**, 2509 (1921).
(22) S. Tanimoto, M. Ohsone, and R. Octa, *Kogyo Kagatsu Zasski*, **69**, 2015 (1966); *Chem. Abstr.*, **67**, 43737 (1967).
(23) E. Boyland and P. Sims, *J. Chem. Soc.*, 980 (1954).
(24) F. Henrich, *Chem. Ber.*, **54**, 2510 (1921).
(25) F. Henrich and O. Rhodius, *Chem. Ber.*, **35**, 1481 (1902).

Scheme I

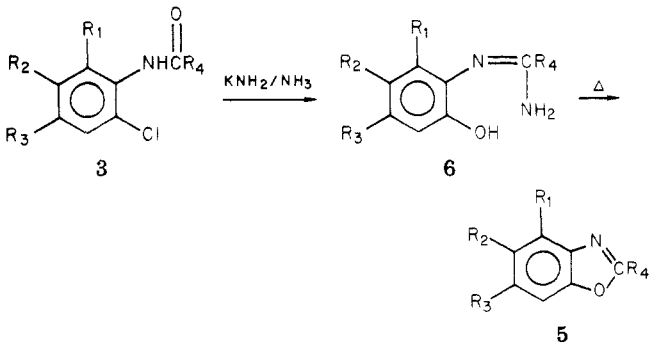


hydrochloric acid solution in quantitative or 80% yield, respectively. However, hydrolysis of **6a** in 10% (v/w) sodium hydroxide solution yielded a complex mixture containing *o*-aminophenol and other unidentified materials.

Finally, 2-phenylbenzoxazole, **5a**, was converted also to **6a** when treated under the same aryne-forming conditions



(potassium amide in liquid ammonia) as the aryne reaction of *o*-chlorobenzamide. A mechanism consistent with these facts is shown in Scheme I. *o*-Chlorobenzamide, **3a**, is converted initially to the corresponding aryne intermediate, **4a**. Ring closure of **4a** yields 2-phenylbenzoxazole, **5a**, which undergoes nucleophilic additon of amide ion to the carbon atom of the C=N bond and subsequent ring-opening at the C—O bond. Neutralization of the resulting ring-opened ion affords **6a**. The remaining haloamides **3b–j**, listed in Table I, were treated with potassium amide in liquid ammonia and all of these amides yielded the corresponding *N*-(*o*-hydroxyaryl)benzamide derivatives, **6b–j**. IR, ^{1}H NMR, and mass spectra of **6b–j** were consistent with assigned structures. Only a few of these compounds could be isolated in pure form as their hydrochloride salts; satisfactory elemental analyses were obtained for these substances. Sublimation of intermediates **6** yielded the corresponding benzoxazole **5** in good to excellent yields. Certain physical properties of hydroxy



amidines **6** and benzoxazoles **5** and the overall yields of **5** from chlorobenzamides **3** are listed in Table I.

This study had demonstrated that the ring-closure aryne reaction is a general one for the preparation of both benzoxazoles and *N*-(hydroxylaryl)benzamidines. Aminobenzamides, which would have been formed by amide addition to the corresponding aryne intermediate, were not observed in any reaction studied.

Experimental Section

Melting points were taken on a Fisher-Johns melting block and are uncorrected. Mass spectra were recorded on a Du Pont 321 GC/MS instrument. ^{1}H NMR sepctra were recorded on a Perkin-Elmer R-32 NMR spectrophotometer; chemical shifts (δ) are expressed in parts per million relative to Me_4Si. IR spectra (KBr disks) were recorded on a Perkin-Elmer 2F3 infrared spectrophotometer. High-pressure liquid chromatographic (HPLC) analyses were performed on a Waters liquid chromatograph equipped with a Model 440 absorbance detector and a 25-cm C_{18}-μBondapak column, using 80% acetonitrile–water solvent at a flow rate of 1 mL/min. TLC was performed on silica gel plates, using 25/75 (v/v) pentane/benzene as the developing solvent. Microanalyses were carried out at Galbraith Laboratories, Knoxville, TN.

Starting Materials. The isomeric toluic acids and chloroanilines were obtained from Eastman Chemical Co.; *o*- and *m*-bromoanilines, 4-methyl-2-bromoaniline, α-naphthoic acid, benzoyl chloride, and β-naphthoyl chloride were obtained from Aldrich Chemical Co. and were used as received. All other acid chlorides were prepared inthe usual manner by treating the corresponding acid with refluxing $SOCl_2$ until the evolution of HCl and SO_2 was complete. Halobenzamides, **6**, were prepared by the Schotten–Bauman reaction.[26] Potassium was obtained from Baker Chemical Co.

General Procedure. A. Preparation of *N*-(Hydroxyaryl)benzamidines (6). Liquid ammonia (250 mL) was condensed into a 1-L, three-necked flask equipped with mechanical stirrer and dry ice condenser. A few small crystals of ferric nitrate were placed in the flask and potassium metal (0.12 mol) was added in portions over a period of 10 min. When initially added, the solution turned bright blue. On complete conversion of potassium to potassium amide the color turned gray. The halobenzanilide, **3** (0.0217 g), was then added in small portions as quickly as possible and the reaction was stirred for 1 h. At this time, the reaction mixture was quenched by the careful addition of NH_4Cl (0.13 mole), the ammonia was evaporated by heating on a steam bath, the solid residue was extracted with acetonitrile (200 mL), and the mixture was filtered. Rotary evaporation of the mother liquor yielded *N*-(hydroxyaryl)benzamidines, **6**. These compounds were dissolved in a minimum amout of 6 N hydrochloric acid and placed in refrigerator overnight, during which time crystals of their hydrochloride salt precipitated. The crystals were dissolved in 25 mL of methanol, ether was added dropwise until the mixture appeared cloudy, and the mixture was placed in the refrigerator overnight. The purified crystals of **6** were collected by filtration and dried prior to chemical, spectral, and elemental analyses.

B. Conversion of *N*-(Hydroxyaryl)benzamides (6) to Benzoxazoles (5). 1. Sublimation Method. The *N*-(hydroxyaryl)benzamides, **6**, were heated at 150 °C (0.01 torr) in a typical vacuum sublimation apparatus equipped with water-cooled finger condenser. The benzoxazole, **5**, which formed under these conditions sublimed and was removed periodically from the sides of the condenser.

2. Acid Hydrolysis. Compound **6** was refluxed with 100 mL of 10% hydrochloric acid for 18 h. The conversion of **6** to benzoxazole, **5**, was monitored by TLC. Upon cooling, the mixture was extracted with ether, and the ester was dried ($MgSO_4$) and evaporated to yield **5**.

3. Basic Hydrolysis. Compound **6** was treated with refluxing 10% sodium hydroxide for 18 h. Monitoring of the reaction during this time by TLC indicated several compounds were formed, but none was **5**. The major spot had an R_f value identical with that of *o*-aminophenol.

Reaction of 2-Phenylbenzoxazole (5a) with Potassium Amide. To 250 mL of liquid ammonia containing 0.12 mol of potassium amide, prepared in a manner described in the general procedure, was added 0.22 mol of **5a**. After being stirred for 30 min, the reaction mixture was quenched by the addition of NH_4Cl (0.13 mol), the ammonia evaporated, and the residue extracted

(26) A. I. Vogel, "Practical Organic Chemistry", John Wiley and Sons, New York, 1962, p 582.

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]

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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

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(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