Selenium-Sulfur Analogs. 7. Synthesis and Characterization of 4-Aralkyl-1,3-selenazoles and -1,3-thiazoles

Robert N. Hanson

Section of Medicinal Chemistry, College of Pharmacy and Allied Health Professions,
Northeastern University, and Joint Program in Nuclear Medicine,
Department of Radiology, Harvard Medical School, Boston, MA 02115

Received March 17, 1983

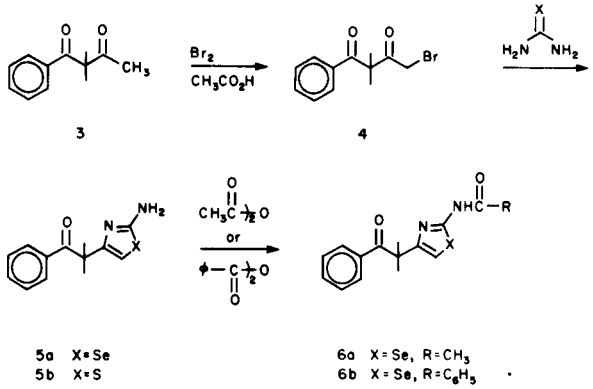
The diketones **3** and **7** were brominated to give the bromomethyldiketones **4** and **8** which were condensed with selenourea and thiourea to give the corresponding 2-amino-1,3-selenazoles **5a, 9a** and 2-amino-1,3-thiazoles **5b, 9b**. Reaction with acetic anhydride and benzoic anhydride yielded the 2-acylated derivatives. Biologic evaluation of these compounds indicated some activity as adrenocortical enzyme inhibitors, but significantly less than that of metyropone.

J. Heterocyclic Chem., **21**, 57 (1984).

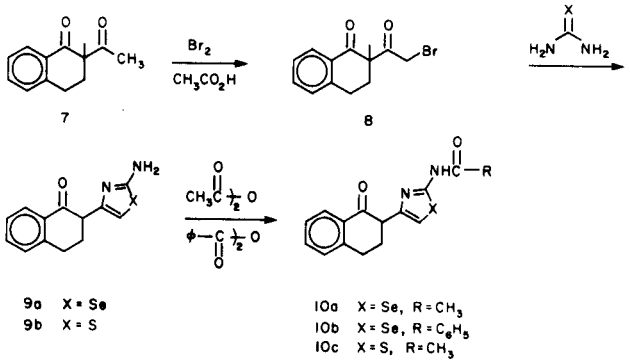
As part of a program to develop radiodiagnostic agents for the gamma scintigraphic imaging of the adrenal cortex, our efforts have focused on the synthesis of radiolabeled derivatives of drugs that inhibit the adrenal corticosteroid biosynthetic enzymes. Two of these 2-methyl-2-(3-pyridyl)-1-phenylpropan-1-one (**1**) [1] and 2-methyl-2-(3-pyridyl)-1,2,3,4-tetrahydronaphthalen-1-one (**2**) [2] (Figure 1) are potent inhibitors of the 11β- and 17α-hydroxylase enzymes, respectively. Initially the 2-(3-pyridyl) moiety was replaced by a 1,2,3-selenadiazolyl group incorporating selenium-75 [3]; the tissue distribution data showed poor adrenal to nontarget tissue ratios suggesting that the heterocyclic ring was unstable *in vivo* [4].

In the present investigation we proposed to replace the pyridyl group with the aminoselenazole and aminothiazole ring systems. The rationale for this substitution was based on two factors. First, the selenazole and thiazole ring systems are chemically more stable than the corresponding selenadiazole or thiadiazole analogs, and therefore should demonstrate more stability *in vivo*. Second, there would be two potential sites for the introduction of a gamma ray emitting radionuclide. The selenazole ring could be prepared either using selenium-75 labeled selenourea or the 2-amino group could be functionalized with an iodobenzoyl group labeled with iodine-123 or -131. Before preparing the radiolabeled compounds, however, it would be necessary to demonstrate the feasibility of their synthesis and their ability to bind to the target enzymes.

Scheme 1



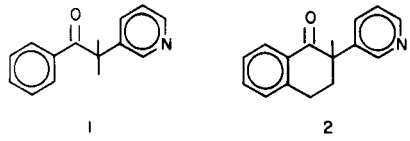
Scheme 2



We wish to report the synthesis, characterization and preliminary bioevaluation of the 4-aralkyl-2-amino-1,3-selenazoles **5a, 9a** and -1,3-thiazoles **5b, 9b** and several of their 2-acylated derivatives. The compounds **5a** and **5b** were prepared in a two step sequence starting from the diketone **3** (Scheme 1). Bromination with bromine in acetic acid gave the bromomethyl diketone **4** in 50% yield. Condensation with selenourea or thiourea gave the desired 2-aminoazoles in high yields. Acylation of **5a** with acetic anhydride and with benzoic anhydride provided the aryl derivatives **6a** and **6b**. In a similar manner the 2-methyl-2-(1-ethanoyl)-1,2,3,4-tetrahydronaphthalen-1-one **7** was converted to the bromomethyl diketone **8** in 73% yield. Condensation with selenourea or thiourea gave the corresponding 2-aminoselenazole **9a** and 2-aminothiazole **9b** in good yields. As above, acetylation or benzoylation provided the desired acylated products **10a-10c** (Scheme 2).

Characterization of the compounds indicated few differences in the infrared spectra between the selenium and sulfur isosteres. The nmr spectra did, however, show the expected downfield shift of the 5-proton of the selenazole

compared to that of the thiazole. This shift has been described previously in our studies [3,5] as well as by others [6,7].



1 2

Figure 1

The compounds were screened as potential enzyme inhibitors in an assay system which compared their ability to bind to a cytochrome P-450 enzyme isolated from the cortex of bovine adrenals relative to that of metyrapone, a potent adrenocorticosteroid enzyme inhibitor [8-10]. The unsubstituted 2-aminoselenazoles and 2-aminothiazoles showed low activity even at the highest concentrations tested. The acylated derivatives were somewhat more active, although none was as active as metyropone. The benzoylated derivative **6b** showed the greatest degree of binding. Therefore, the iodobenzoyl analogs of **6b** and **10b** will be prepared for future radiolabeling and tissue distribution studies.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover meltemp apparatus using open capillaries and are uncorrected. The nmr spectra were obtained with a Varian T-60 instrument using tetramethylsilane as the internal standard. The ir spectra were recorded on a Beckman IR-10 spectrograph. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

General Procedure for the Preparation of the Monobromomethyl Diketones.

To the diketone dissolved in glacial acetic acid was added a solution of

Table 1

Compound	% Yield	Mp °C	Spectral Data: NMR (δ downfield from TMS) [a]	Spectral Data: IR (potassium bromide) (cm^{-1})	Molecular Formula	Elemental Analysis Calcd./Found: C	H	N
5a	53	201-204	1.45 (6H, s), 3.25 (2H, s), 6.78 (1H, s), 7.02-7.67 (5H, m)	3400, 3100, 2960, 2920, 1665, 1630, 1525, 1310, 1255, 940	$C_{13}H_{14}N_2OSe$	53.25 53.44	4.81 5.09	9.56 9.25
5b	73	189-191	1.55 (6H, s), 4.28 (2H, s), 6.28 (1H, s), 7.22-7.57 (5H, m)	3400, 3130, 2960, 2920, 1670, 1630, 1520, 1330, 1255, 950	$C_{13}H_{14}N_2OS$	63.44 62.69	5.73 5.79	11.37 11.63
6a	87	173-175	1.57 (6H, s), 2.20 (3H, s), 7.17-7.60 (5H, m), 7.33 (1H, s)	3250, 2980, 2930, 1655, 1545, 1275, 1250	$C_{15}H_{16}N_2O_2Se$	53.74 53.64	4.81 5.13	8.35 8.20
6b	81	188-190	1.62 (6H, s), 7.07-7.60 (7H, m), 7.67-8.13 (4H, m)	3270, 3070, 2970, 1665, 1540, 1290, 1255	$C_{20}H_{18}N_2O_2Se$	60.46 60.53	4.57 4.80	7.05 7.09
9a	71	160-163	1.43 (3H, s), 1.83-2.27 (1H, m), 2.77-3.00 (2H, m), 3.17 (1H, s), 6.30 (1H, s), 6.70 (2H, s), 7.06-7.43 (3H, m), 7.87-8.03 (1H, m)	3380, 3030, 2930, 2890, 1660, 1620, 1510, 1290, 1210	$C_{14}H_{14}N_2OSe$	55.09 55.16	4.62 4.75	9.17 9.14
9b	73	160-163	1.43 (3H, s), 1.90-2.27 (1H, m), 2.70-3.00 (2H, m), 3.10 (1H, s), 5.81 (1H, s), 6.17 (2H, s), 7.00-7.37 (3H, m), 7.87-8.00 (1H, m)	3410, 3100, 2950, 2920, 1680, 1620, 1530, 1330, 1230	$C_{14}H_{14}N_2OS$	65.09 65.08	5.46 5.62	10.84 10.96
10a	87	220-222	1.53 (3H, s), 1.90-2.37 (1H, m), 2.20 (3H, s), 2.70-2.97 (2H, m), 6.93 (1H, s), 7.03-7.37 (3H, m), 7.93-8.05 (1H, m)	3420, 3260, 3220, 3075, 2960, 2920, 1685, 1660, 1590, 1540, 1280, 1230	$C_{16}H_{16}N_2O_2Se$	55.35 55.38	4.65 4.74	8.06 8.10
10b	70	158-161	1.55 (3H, s), 1.93-2.35 (1H, m), 2.76-3.00 (2H, m), 3.13 (1H, s), 7.08-7.53 (7H, m), 7.80-8.18 (3H, m)	3480, 3270, 3060, 2960, 2920, 1660, 1595, 1530, 1280, 1220	$C_{21}H_{18}N_2O_2Se$	61.61 60.91	4.43 4.51	6.84 7.18
10c	51	173-176	1.53 (3H, s), 1.90-2.37 (1H, m), 2.20 (3H, s), 2.67-3.00 (2H, m), 6.42 (1H, s), 6.93-7.33 (3H, m), 7.90-8.07 (1H, m)	3390, 3040, 2950, 2910, 1670, 1655, 1540, 1290, 1220	$C_{16}H_{16}N_2O_2S$	63.99 63.97	5.37 5.30	9.32 9.19

[a] Deuteriochloroform.

bromine in glacial acetic acid. The resulting reaction was stirred at ambient temperature for 3 hours, poured into water and extracted twice with ether. The ether layers were combined, washed with a 50% sodium bicarbonate solution and evaporated to dryness. The oil was then chromatographed on silica gel and eluted with increasing concentrations of methylene chloride in hexane. This gave a relatively clean separation of the dibromomethyldiketone, the monobromomethyldiketone, and the starting material. The isolated yields of the pure monobromomethyl diketones ranged from 51-73%.

General Procedure for the Preparation of the 2-Amino-1,3-selenazoles and 2-Amino-1,3-thiazoles.

To a solution of the bromomethyl diketone in acetonitrile was added the selenourea or thiourea (5% molar excess). The reaction mixture was heated at reflux for 4 hours, cooled to ambient temperature and evaporated to dryness. The residue was partitioned between an organic phase consisting of chloroform:2-propanol (3:1) and 5% aqueous sodium bicarbonate. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The residue was dissolved in hot 2-propanol and the product precipitated upon cooling. The isolated yields of **5a**, **5b**, **9a** and **9b** ranged from 71-73%.

General Procedure for the Acetylation of the 2-Amino-1,3-selenazoles and 2-Amino-1,3-thiazoles.

The aminoselenazole or aminothiazole (1.5-2.0 mmoles) was dissolved in 2 ml of acetic anhydride. The reaction was heated at reflux for 2 hours, then allowed to cool to ambient temperature. The reaction solution was added to 50 ml of water to hydrolyze the excess acetic anhydride. The resulting mixture was partitioned between chloroform and 10% aqueous sodium bicarbonate. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The product was recrystallized from 2-propanol. The isolated yields of **6a**, **10a**, and **10c** ranged from 51-87%.

Procedure for the Benzoylation of **9a**.

To a solution of **9a** (1.3 mmoles) in 20 ml of acetonitrile was added benzoic anhydride (1.5 mmoles). The solution was heated at reflux for 4 hours, cooled to ambient temperature and evaporated to dryness. The residue was partitioned between chloroform and 10% aqueous sodium bicarbonate. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was recrystallized from 2-propanol to give **10b** in 70% yield.

Acknowledgement.

The author is grateful to Dr. H. A. Salhanick, Harvard University School of Public Health, for performing the biologic assays of the test compounds. This project has been supported in part by DOE Contract DE-AC02-76EV04115, a grant from the Jane Coffin Child Memorial Fund, and NIH Grant CA 19898.

REFERENCES AND NOTES

[1] J. L. Napoli and R. E. Counsell, *J. Med. Chem.*, **20**, 762 (1977).

[2] W. L. Bencze and L. D. Barsky, *J. Med. Pharm. Chem.*, **5**, 1298 (1962).

[3] R. N. Hanson and M. A. Davis, *J. Heterocyclic Chem.*, **17**, 1245 (1980).

[4] R. N. Hanson and M. A. Davis, *J. Pharm. Sci.*, **70**, 91 (1981).

[5] R. N. Hanson and M. A. Davis, *J. Heterocyclic Chem.*, **18**, 205 (1981).

[6] E. Barni, G. DiModica and A. Gasco, *ibid.*, **4**, 139 (1967).

[7] U. Svanholm, *Acta Chem. Scand.*, **26**, 459 (1972).

[8] V. I. Uzgiris, P. E. Graves, M. Querner, K. Kashiwagi, E. N. McIntosh and H. A. Salhanick, *Biochemistry*, **16**, 593 (1977).

[9] P. E. Graves, V. I. Uzgiris and H. A. Salhanick, *Steroids*, **35**, 543 (1980).

[10] C. A. Whipple, R. L. Grodzicki, J. Hourihan and H. A. Salhanick, *ibid.*, **37**, 673 (1981).