Selenium-Sulfur Analogs 2. Synthesis and Characterization of 4-Aralkyl-1,2,3-selenadiazoles and -1,2,3-Thiadiazoles

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The 1,3-diketones **5** and **8** were alkylated with methyl iodide to give the nonenolizable diketones **6** and **9** which condensed with semicarbazide hydrochloride yielding the monosemicarbazones **7** and **10**. Cyclization with selenous acid or with thionyl chloride led to the corresponding 1,2,3-selenadiazoles **3a**, **4a**, and 1,2,3-thiadiazoles **3b**, **4b**.

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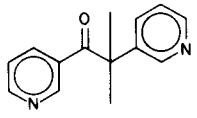
Recent approaches to the development of radiodiagnostic agents for the gamma scintigraphic imaging of the adrenal cortex have focused on the preparation of labeled drugs that inhibit the adrenal corticosteroid biosynthetic enzymes (1). Tritium labeled 2-methyl-2-(3-pyridyl)-1-phenylpropan-1-one **1** (2) and 2-methyl-2-(3-pyridyl)-1,2,3,4-tetrahydronaphthalen-1-one **2** (3), which are inhibitors of 11β- and 17α-hydroxylase respectively, have been shown to localize in the adrenal cortex of dogs and humans (4,5). Efforts have been made to prepare



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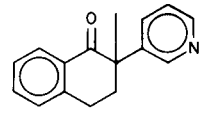

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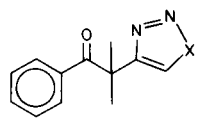
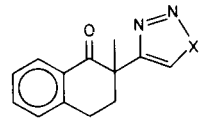
gamma-ray or positron emitting analogs. The short half-lives of the positron emitting nuclides, ^{11}C (20 minutes), ^{13}N (10 minutes) and ^{15}O (2 minutes), preclude their use in extensive radiopharmaceutical syntheses. The broad organic applications of selenium (6) suggest that nitrogen-selenium-containing heterocyclic analogs of **1** and **2** could be more readily prepared, and the availability of the selenium-75 radionuclide (t ½ = 120 days) would permit their subsequent biologic evaluation. Because similar methods are often used to make sulfur and selenium analogs and because the synthesis of compounds with both congeners would provide a direct comparison of their physical and spectroscopic properties, we undertook the preparation of the 1,2,3-selenadiazoles **3a**, **4a** and the 1,2,3-thiadiazoles **3b**, **4b** which are structural analogs of the enzyme inhibitors **1** and **2**.



3a, X = Se
3b, X = S



4a, X = Se
4b, X = S

The rationale for the choice of the 1,2,3-selenadiazole and 1,2,3-thiadiazole ring systems was based on two considerations. First, the heterocyclic ring could be easily formed with the selenium or sulfur atom incorporated in the last step of the sequence, a valuable condition in any subsequent radioactive synthesis. The preparation of a variety of simple 1,2,3-selenadiazoles and 1,2,3-thiadiazoles involving the oxidative cyclization of a semicarbazone with selenous acid or thionyl chloride has been described (7-14). Second, the molecular dimensions and the electron deficient character of the ring systems are roughly equivalent to those of pyridine and therefore, substitution of the heterocycle for the pyridine moiety of **1** and **2** should result in only a minor perturbation of the biologic properties.

In this paper we wish to report the synthesis and characterization of 2-methyl-2-(4-1,2,3-selenadiazolyl)- and 2-methyl-2-(4-1,2,3 thiadiazolyl)-1-phenylpropan-1-one **3a,b**, and 2-methyl-2-(4-1,2,3-selenadiazolyl)- and 2-methyl-2-(4-1,2,3 thiadiazolyl)- 1,2,3,4-tetrahydronaphthalen-1-one **4a,b**. Compound **3a** was prepared in a three step synthetic sequence which started with 1-phenylbutane-1,3-dione **5** (Scheme 1). Alkylation of the diketone with methyl iodide gave the *gem*-dimethyl product **6** which was isolated in 65% yield. The condensation of **6** at the less hindered carbonyl with one equivalent of semicarbazide gave a 59% yield of the monosemicarbazone **7**. The absorption in the nmr spectrum for the terminal methyl group was shifted upfield 0.32 δ relative to that of **6** while there was virtually no change in the absorption of the protons ortho to the aromatic ketone. This evidence and the disappearance of the isolated aliphatic ketone absorption at 1705 cm^{-1} in the infrared spectrum established the site of condensation. The reaction of the semicarbazone **7** with selenous acid at 60° gave a 60% yield of the desired 1,2,3-selenadiazole **3a**. The product obtained as irridescent green crystals was stable for several months in the dark at room temperature. Cyclization with thionyl chloride at 0-25° gave the corresponding 1,2,3-thiadiazole

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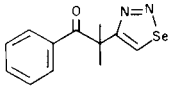
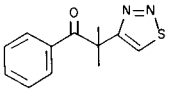
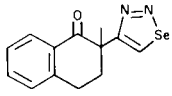
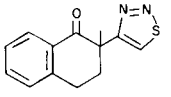
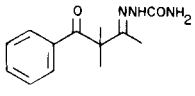
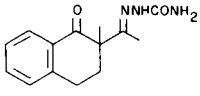
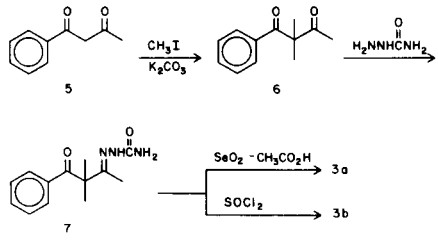
Table 1

Compound		M.p. °C	Yield %	Spectral Data: Nmr δ Downfield from TMS	Spectral Data: Ir (Cm^{-1})	Elemental Analysis: Calcd. C	Calcd. H	Found C	Found H
3a		130-132	58	1.88 (s, 6H), 7.17-7.57 (a) (m, 5H), 9.00 (s, 1H)	3100, 3000 (m) (b), 1670 (s), 1220 (s)	51.61	4.30	51.89	4.32
3b		97-98	15	1.85 (s, 6H), 7.22-7.55 (a) (m, 5H), 8.25 (s, 1H)	3070, 3000 (m) (b), 1675 (s), 1245 (s)	62.07	5.17	62.42	5.49
4a		oil	38	1.76 (s, 3H), 2.13-2.58 (a) (m, 1H), 2.80-3.17 (m, 3H), 7.11-7.52 (m, 3H), 8.08-8.23 (m, 1H), 8.89 (s, 1H)	3100, 2940 (m) (c), 1680 (s), 1600 (s), 1220 (s)	53.61	4.16	d	d
4b		oil	10	1.73 (s, 3H), 2.22-2.75 (m, 1H) (a), 2.80-3.18 (m, 3H), 7.05-7.55 (m, 3H), 7.97-8.15 (m, 1H), 8.15 (s, 1H)	3070, 2920 (m) (c), 1680 (s), 1600 (s), 1230 (s)	64.34	4.92	63.96	5.24
7		170-172	59	1.43 (s, 6H), 1.75 (s, 3H) (e), 5.93 (broad, 2H) 7.33-7.53 (m, 3H) 7.73-7.90 (m, 2H)	3480 (s) (b), 3105 (m), 1675-1685 (s), 1580 (s)	63.11	6.93	62.91	7.02
10		218-220	55	1.37 (s, 3H), 1.88 (s, 3H) (e), 2.07-2.40 (m, 1H) 2.85-3.10 (m, 3H), 5.52 (broad, 2H), 7.13-7.50 (m, 3H), 7.88-8.05 (m, 1H)	3460 (s) (b), 3200 (m), 1680-1690 (s), 1580 (m)	64.86	6.56	64.55	6.71

(a) Deuteriochloroform. (b) Potassium bromide. (c) Neat. (d) Instability of compound precluded elemental analysis. (e) Deuteriochloroform plus DMSO-d_6.

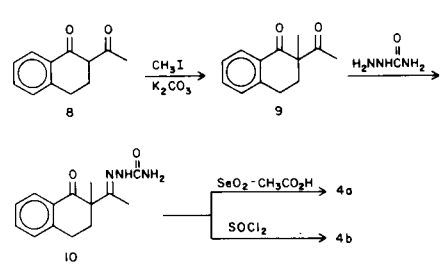
3b in only 10-15% yield with the major product being an uncyclized material. Elevation of the reaction temperature did not increase the yield.

Scheme I

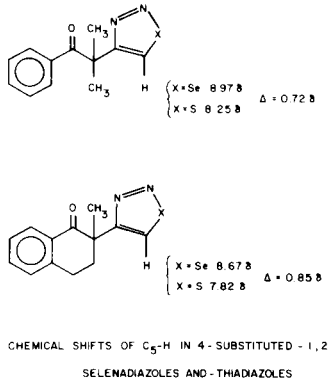


The 2-methyl analogs of **2** (**4a,b**) were prepared as indicated in Scheme 2. Alkylation with methyl iodide gave the racemic intermediate **9** which underwent condensation with semicarbazide at the less hindered carbonyl to yield the monosemicarbazone **10**. Support for this proposed structure was provided by the nmr spectrum in which the terminal methyl group was shifted upfield δ 0.32 compared to that of the starting material. Subsequent oxidation with selenium dioxide in acetic acid gave the desired 1,2,3-selenadiazole **4a** which was isolated as a pure yellow oil. Compound **4a** was unstable under ambient conditions as evidenced by the rapid appearance of red metallic selenium; storage at 0° in the dark retarded the decomposition. Characterization of the product by ir, nmr and mass spectrometry was performed on freshly purified samples. The 1,2,3-thiadiazole **4b** was prepared in 9-12% yield by cyclization in thionyl chloride. The resulting yellow oil was stable under ambient conditions (air, light, 25°) for several weeks.

Scheme 2



The comparison of the corresponding 1,2,3-selenadiazoles **3a,4a** and 1,2,3-thiadiazoles **3b,4b** indicates that there are slight differences between the analogs. The thiadiazoles are more stable than the selenadiazoles, as **3b** and **4b** show no evidence of decomposition over 3 to 4 weeks under ambient conditions whereas red selenium is evident after several days for **4a** and 3 to 4 weeks for **3a**. Chromatographic behavior on alumina and silica gel are vitually identical and the infrared spectra are very similar, except for slight variations in the 930-990 and 1280-1340 cm^{-1} regions. The most striking difference between the selenadiazoles and the thiadiazoles is the chemical shift of the C_5-H proton on the heterocyclic ring. In the selenadiazoles the absorption is shifted δ 0.72-0.85 downfield relative to that of corresponding sulfur analog (Figure 1). The same effect has been reported for 1,3,4-selenadiazoles (15) and benzoselenazoles (16) and is attributed to the increased deshielding of the selenium atom with respect to that of sulfur.



CHEMICAL SHIFTS OF C_5-H IN 4-SUBSTITUTED-1,2,3-SELENADIAZOLES AND-THIADIAZOLES

Figure 1

EXPERIMENTAL

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

General Procedure for the Preparation of the Methylated Diketones.

A mixture consisting of the diketone (20 mmoles), methyl iodide (100% molar excess) and potassium carbonate (40 mmoles) in acetone was heated at reflux for 24 hours. The precipitate was removed by filtration and the filtrate was concentrated to an oil. The oil was chromatographed on alumina (neutral, activity III) and the desired product eluted with hexane-methylene chloride (4:1 v/v) as the first component. The respective yields of **6** and **9** were 65% and 75%.

General Procedure for the Preparation of the Monosemicarbazones.

Two ml. of pyridine were added to a mixture of 10 mmoles of the diketone and 10 mmoles of the semicarbazide hydrochloride in methanol-water (7:3 v/v). The reaction was heated at reflux for 3 hours, cooled, added to 25 ml. of water, and extracted with chloroform. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness. The crude product was crystallized from isopropanol to give the pure monosemicarbazone.

General Procedure for the Preparation of the 1,2,3-Selenadiazoles.

A solution composed of 2.0 mmoles of the monosemicarbazone and 2.0 mmoles of selenium dioxide in 3 ml. of glacial acetic acid was heated at 60° for one hour. The reaction mixture was added to 10 ml. of water and extracted with chloroform. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness. Purification by silica gel column chromatography using chloroform as eluent gave the pure 1,2,3-selenadiazoles **3a,4a**.

General Procedure for the Preparation of the 1,2,3-Thiadiazoles.

Two mmoles of the monosemicarbazone were added to 2 ml. of cold thionyl chloride. The reaction was stirred at 0-5° for 30 minutes and then allowed to warm to room temperature. The excess thionyl chloride was removed and the resulting oil was partitioned between chloroform and 5% sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness. The oil was chromatographed on silica gel using chloroform as eluent to give the pure 1,2,3-thiadiazoles. Compound **3b** was isolated as an oil that crystallized on standing and **4b** as a yellow oil.

Acknowledgment.

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