Project 1B

Section 2: Adrenal Imaging Agents

ABSTRACT

The goals of this proposal are the development of selenium-containing analogs of the aromatic amino acids as imaging agents for the pancreas and of the adrenal cortex enzyme inhibitors as imaging agents for adrenal pathology. The objects for this year included (a) the synthesis of methylseleno derivatives of phenylalanine and tryptophan, and (b) the preparation and evaluation of radiolabeled iodobenzoyl derivatives of the selenazole and thiazole analogs of metyrapone and SU-9055.

PROGRESS REPORT

I. Objectives

The aims of the project are the synthesis of selenium-containing analogs of the aromatic amino acids for pancreatic imaging and of selenium-containing analogs of adrenal cortex enzyme inhibitors for adrenal imaging, the initial evaluation of these analogs in a rat model and the further evaluation of the more promising agents, i.e., organ distribution and pharmacokinetics, in larger animals in preparation for clinical trials.

The goals for the current year included (a) the synthesis of methylseleno derivatives of phenylalanine and tryptophan, and (b) the synthesis and evaluation of the iodobenzamido selenazole and thiazole analogs of metyrapone and SU-9055.

II. Work in Progress

A. The synthesis of methylseleno derivatives of aromatic amino acids

The synthesis of the 3- and 4-methylseleno derivatives of phenylalanine are shown in Figure 1. The reactions were straightforward and gave the desired products in good overall yields. The amino acids were characterized by IR, NMR, UV and elemental analysis.

The synthesis of the 5- and 6-methylseleno tryptophans are shown in Figure 2. The synthesis of the 5-methylseleno compound was complicated to some extent by the decreased reactivity of the selenocyanate toward methyl magnesium bromide. Separation of the desired intermediate from the starting material was necessary before completing the synthetic sequence.

B. Synthesis of a selenadiazole analog of phenylalanine

The 1,2,5-selenadiazole analog of phenylalanine was prepared via a five-step sequence as described in Figure 3. The yields in the first two steps were low (<30%), but the final compound has the potential for labeling via direct ^{75}Se-Se exchange of the amino acids.

C. Biologic Evaluation

The biologic distribution of the selenium-containing amino acids in rats is being determined by both neutron activation and x-ray fluorescence of the liver and pancreas.

D. Synthesis and evaluation of the iodobenzamido selenazole and thiazole analogs of metyrapone and SU-9055

The synthesis of the radioiodinated iodobenzamido-selenazole and thiazole analogs of metyrapone and SU-9055 are shown in Figure 4. The syntheses were straightforward and proceeded in good yield. The target compounds were characterized by IR, NMR, and elemental analysis. They were labeled by exchange in 80-95% yield to give specific activities in the 1.6-10.0 Ci/mmol range. The radiochemicals were dissolved in propylene glycol and administered i.v. to normal rats. The organ distributions were determined at 5, 15, 60 and 120 minutes, and the tissue concentrations are shown in Table 1. The highest concentrations for both the metyrapone and SU-9055 analogs were in the adrenals and liver with somewhat less in the kidneys. The tetralone derivatives (SU-9055 analogs) had higher adrenal concentrations than the corresponding metyrapone analogs. This was also reflected in the adrenal to blood ratios (Figure 5), the SU-9055 analog (x=Se) having the highest ratio over the time period examined. Attempts to image the adrenals of rabbits and dogs using the ^{131}I-labeled analogs were unsuccessful, because of high background in the gastrointestinal tract (hepatobiliary excretion).

III. Goals

Goals for the coming year include the preparation of radiolabeled derivatives of SU-9055 with lower hepatobiliary excretion, their evaluation in normal rats and rabbits, and the preparation of radioiodinated derivatives of monoamine oxidase inhibitors as potential adrenal medulla imaging agents.

IV. Staffing

Name	Role	% Effort for Report Period	% Effort for Remainder of Current Year
Davis, M.A.	Project Investigator	5	5
Hanson, R.N.	Co-Investigator	10	10
Carmel, A.D.	Research Assistant	10	10
Taube, R.A.	Research Associate	50	50

V. Publications

a. Hanson RN and Davis MA: Selenium-sulfur analogs. 2. Synthesis and characterization of 4-aralkyl-1,2,3-selenadiazoles and -1,2,3-thiadiazoles. J. Heterocyclic Chem. 17:1245-1247, 1980.

b. Hanson RN and Davis MA: Selenium-sulfur analogs. 3. Synthesis and biodistribution of two ^{75}Se-4-substituted-1,2,3-selenadiazoles. J. Pharm. Sci., 1980.

c. Hanson RN and Davis MA: Selenium-sulfur analogs. 4. Synthesis and characterization of (±)-beta-(2-amino-1,3-selenazol-4-yl)alanine. J. Heterocyclic Chem. in press.

Papers Presented

a. Hanson RN and Davis MA: Synthesis and evaluation of radiolabeled azoles as adrenal cortex imaging agents. 178th National American Chemical Society meeting, Washington, DC, September 1979.

b. Hanson RN and Davis MA: Radiolabeled enzyme inhibitors as potential adrenal imaging agents. Third International Symposium on Radiopharmaceutical Chemistry, St. Louis, Missouri, June 1980.

Tal Figure 1. 3- and 4- Methylselenophenylalanines

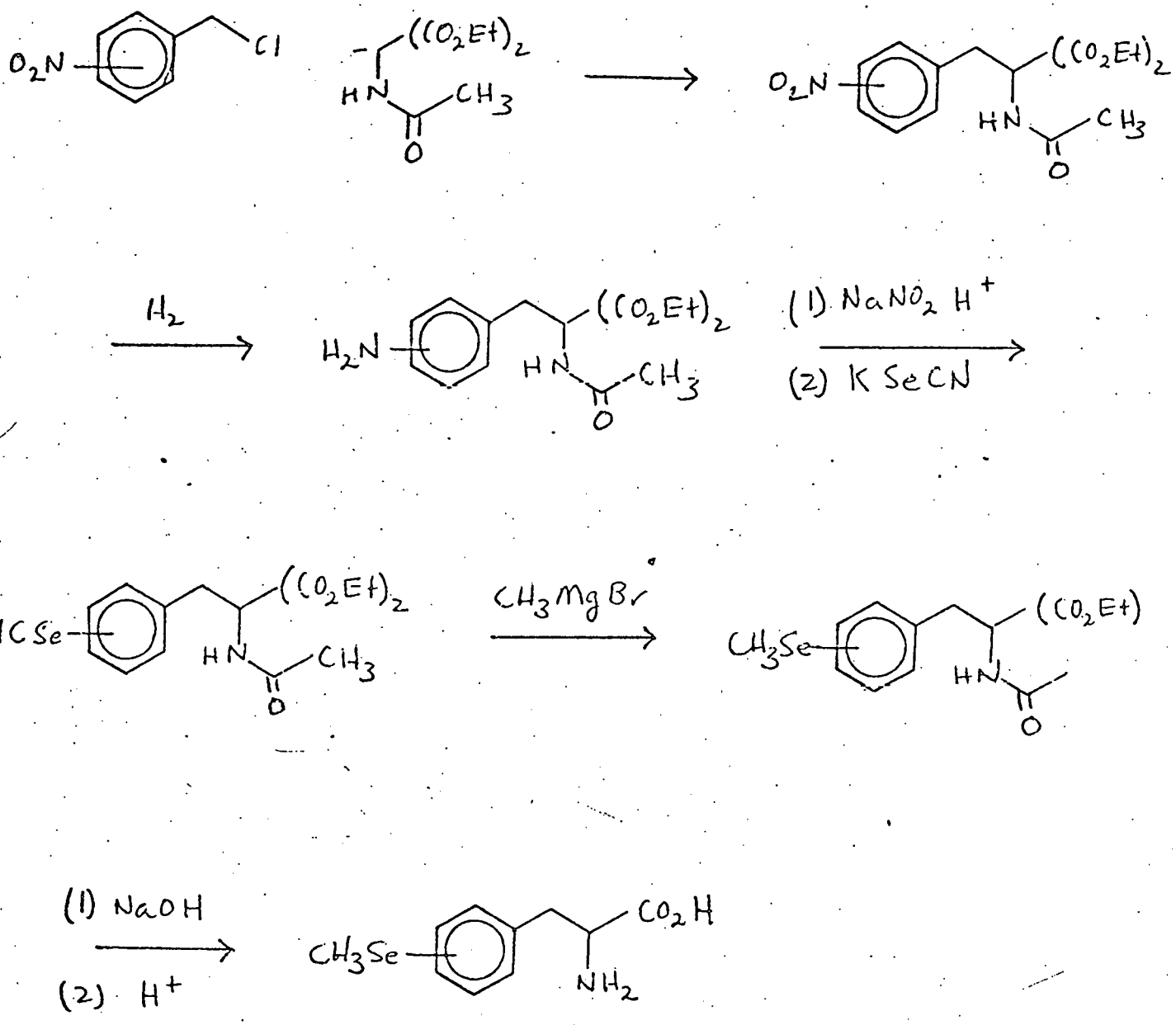
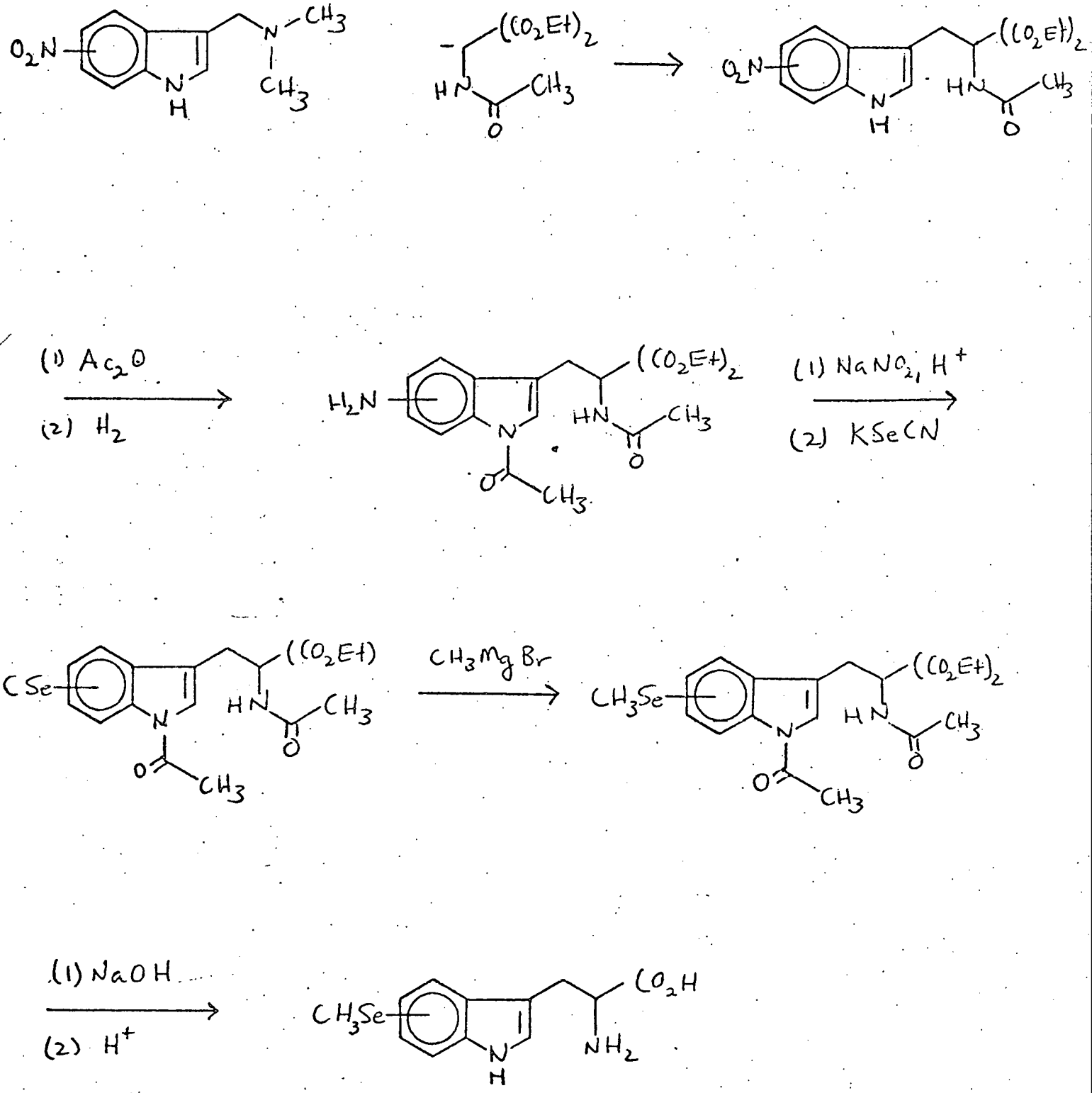


Figure 2. 5-and 6- methylselenotryptophans



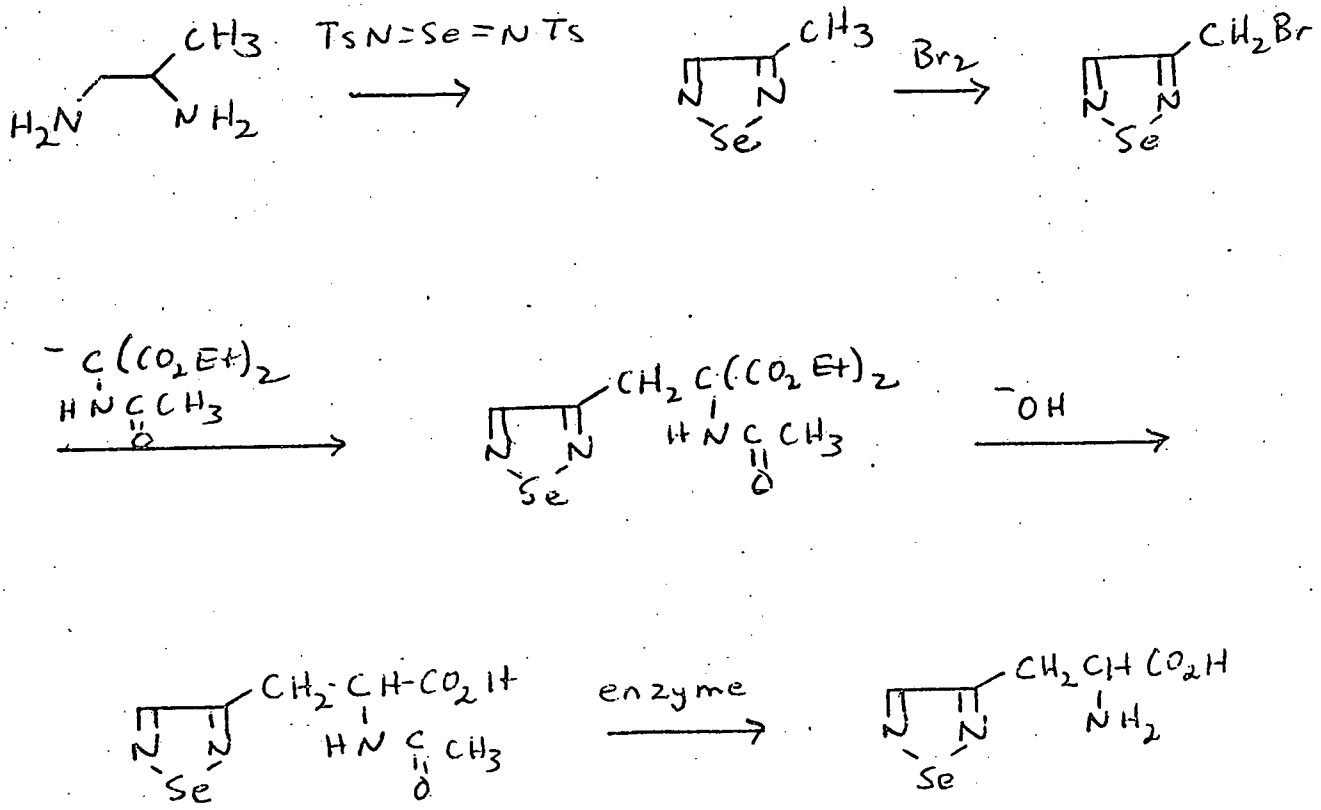
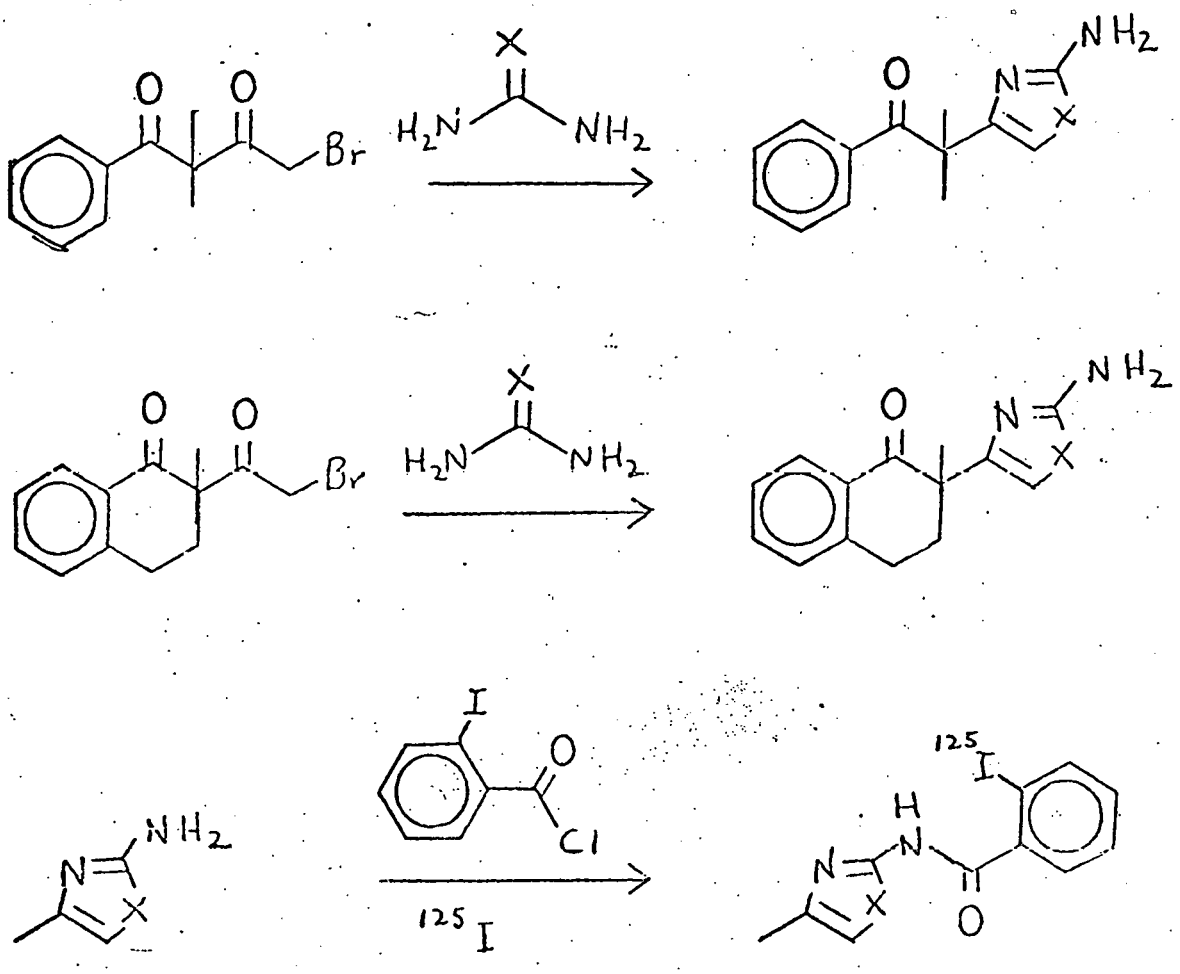

CH3
TsN=Se=NTs
H2N
NH2
CH3
Br2
CH2Br
Se
-C(CO2Et)2
HNCCH3
O
CH2C(CO2Et)2
HNCCH3
O
-OH
CH2-CH-CO2H
HNCCH3
O
enzyme
CH2CHCO2H
NH2

Figure 3



X = S, Se

FIGURE 4

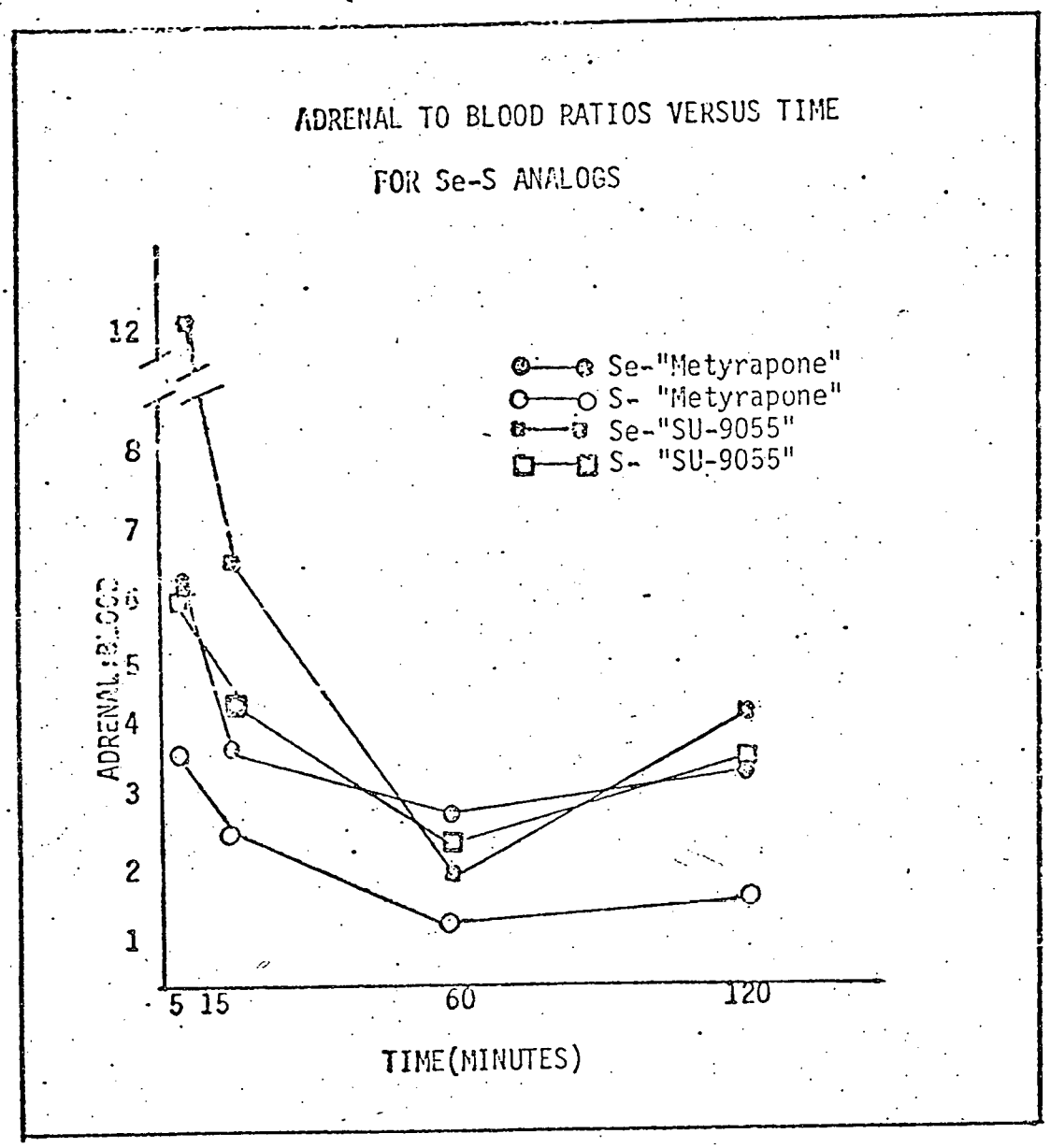

ADRENAL TO BLOOD RATIOS VERSUS TIME
FOR Se-S ANALOGS
Se-"Metyrapone"
S- "Metyrapone"
Se-"SU-9055"
S- "SU-9055"
12
8
7
5
4
3
2
1
5 15
60
120
TIME(MINUTES)

FIGURE 5

TISSUE CONCENTRATIONS (%ID/G) FOR ^{125}I-LABELED

Se AND S ANALOGS

"METYRAPONE" ANALOGS

TIME	TISSUE =	ADRENAL		LIVER		KIDNEY		BLOOD	
		Se	S	Se	S	Se	S	Se	S
5		2.70	1.92	2.85	1.42	1.07	0.62	0.51	0.61
15		1.27	1.55	3.06	1.72	0.56	0.67	0.41	0.76
60		0.95	0.35	1.44	0.59	0.63	0.31	0.41	0.41
120		0.85	0.36	1.24	0.44	0.88	0.24	0.29	0.32
	"SU-9055" ANALOGS								
5		7.42	1.94	4.34	2.17	1.56	0.84	0.62	0.38
15		2.31	1.12	1.58	1.68	0.28	0.49	0.40	0.30
60		0.61	0.63	1.20	1.28	0.49	0.40	0.37	0.31
120		1.00	0.95	0.45	1.14	0.36	0.34	0.28	0.32

TABLE 1