RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Synthesis and Biological Evaluation of Tc-99m N,N′-Bis(mercaptoacetyl)-2,3-diaminopropanoate: A Potential Replacement for [^{131}I]*o*-iodohippurate

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A new technetium-chelating agent based on amide and mercaptide donor groups, N,N′-bis(mercaptoacetyl)-2,3-diaminopropanoate, was synthesized as an analog of previously described N,N′-bis(mercaptoacetyl)ethylenediamine (DADS). Complexation of Tc-99m with the new chelating group resulted in two components that were separable by high-performance liquid chromatography. The component that eluted first demonstrated high specificity for renal excretion, with over 90% in the urine of rabbits at 35 min, 87% in the urine of mice at 2 hr, and 1.6% or less in the intestines of mice. Excretion was rapid, with the first component equaling or exceeding [^{131}I]*o*-iodohippurate in the urine of rabbits at all times. The second or latter component demonstrated comparable specificity but slightly slower renal excretion kinetics. Clinical trials with the first component are probably warranted.

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In 1979 Davison and co-workers (*1*) introduced a new class of chelating agents for technetium, based on amide nitrogen and thiolate sulfur donor groups. A later report presented structural data for the characterized compounds (*2*). The initial report stated that a member of the series, (Tc-99m)N,N′-bis(mercaptoacetyl)ethylenediamine (Tc-DADS), demonstrated rapid renal excretion in animals. With an interest in developing a Tc-99m replacement for [^{131}I]*o*-iodohippurate (OIH) we synthesized the chelating-agent precursor and the Tc-99m complex and studied the biodistribution of Tc-DADS (*3*). In agreement with the earlier results, the complex was found to be rapidly excreted in the urine in a manner consistent with tubular secretion (*3–5*), and appeared to be a potential Tc-99m-labeled replacement for OIH. Animal studies indicated that the rate of renal excretion, while much faster than that of Tc-DTPA, was not as rapid as that of OIH, and that biliary excretion was a significant alternative pathway (*3*). Clinical evaluation of Tc-DADS in renal-transplant patients (*6*) indicated that biological behavior in people with good renal function correlated with the animal data, whereas behavior in patients with reduced renal function was markedly reduced. In such patients, the reduction in renal clearance and excretion was greater than with OIH, studied in the same patients.

We have synthesized several ethylene-bridge analogs of Tc-DADS with the object of obtaining increased tubular-cell specificity and excretion rate. The analogs studied so far have been methyl, hydroxymethylene, benzo, carboxylate, dicarboxylate, and benzocarboxylate. Of those evaluated, a component of the radiochemical mixture derived from the carboxylate analog showed properties significantly superior to those of Tc-DADS and comparable with those of OIH in the above biological parameters. We have therefore carried out a more detailed study of the components resulting from high-pressure liquid chromatography of Tc-99m N,N′-bis(mercaptoacetyl)-2,3-diaminopropanoate (Tc-CO_2-DADS-A and B). The synthesis and biological behavior of the other analogs will be reported later.

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MATERIALS AND METHODS

General. Elemental analyses were obtained commercially.* Proton magnetic resonance (PMR) spectra were obtained† and high-performance liquid chromatographic analyses were done.‡

Synthesis of ethyl N,N'-bis(benzoylmercaptoacetyl)-2,3-diaminopropanoate (ethyl bis-benzoyl-CO_2-DADS). Into a dry flask under nitrogen were placed 1.40 g (0.010 mol) of 2,3-diaminopropionic acid hydrochloride and 250 ml of absolute ethanol. Dry HCl gas was then bubbled into the solution. The mixture was refluxed for one to two days or until PMR analysis of aliquots, with solvent removed, indicated complete formation of the ethyl ester. The product was then concentrated to a dry solid. The hydrochloride ester was dissolved by rapid stirring at icebath temperature in a mixture of 50 ml toluene and 50 ml of saturated sodium bicarbonate. Then 5.0 g (0.044 mol) of chloracetyl chloride in 10 ml of toluene was added dropwise. After addition was complete, the mixture was allowed to come to room temperature and stirred for an additional 30 min. Layers were separated and the aqueous portion extracted twice with ethyl acetate. The organic layers were combined, washed with water and brine, and dried ($MgSO_4$). Removal of solvent left 2.28 g of a white solid (87%). PMR ($CDCl_3$) δ 1.31 (t, 3.0 IH, CH_3), 3.74 (t, 1.9 H, —HNC$\underline{H}_2$CH—), 4.07 (s, 4.0, ClC$\underline{H}_2$NH—), 4.21 (q, 2.0 H, OC$\underline{H}_2CH_3$), 4.67 (broad, 1.0 H, —CH_2—C$\underline{H}$(—NH—)—$CO_2CH_2CH_3$), and 7.12 and 7.58 (broad, 1.0 H each, —CON$\underline{H}$—). The material was used without further purification.

A solution of 1.27 g (4.45 mmol) of the bischloroacetamide was prepared in 10 ml of dry ethanol under nitrogen. To this was added a solution of sodium thiobenzoate in dry ethanol [prepared from sodium ethoxide (204 mg of sodium, 8.87 mmol, in ethanol) which was reacted with 1.23 g (8.90 mmol) of thiobenzoic acid.] After a few minutes at room temperature, precipitation occurred. The reaction was heated to reflux for 30 min. It was then allowed to cool, diluted with ethyl acetate, washed with water and brine, and dried ($MgSO_4$). Removal of solvent left 2.68 g of a cream-colored solid. Recrystallization from toluene gave 1.30 g: mp 129.5-131°; PMR ($CDCl_3$, —$DMSOd_6$) δ 1.20 (t, 3.0 H, $OCH_2C\underline{H}_3$), 3.72 and 3.81 (singlets superimposed on triplet, —COC$\underline{H}_2$S—) and 3.70 (triplet with singlets, —NHC$\underline{H}_2$CH(—NH—)—CO—, 6.0 H combined), 4.10 (q, 2.0 H, —OC$\underline{H}_2CH_3$), 4.60 (broad quartet, 1.0 H, —$CH_2C\underline{H}$—(—NH—)—CO_2), and 6.75-8.15 (complex aromatic and amide H, 12.3 H). Anal: calcd. for $C_{23}H_{24}N_2O_6S_2$: C = 56.56; H = 4.92, N = 5.74, S = 13.11; found: C = 56.64, H = 5.09, N = 5.76, S = 13.26.

Radiolabeling with Tc-99m. The chelating-agent precursor, bis ethylbenzoyl-CO_2-DADS (3 mg), was dissolved in 0.3 ml of ethanol with heating. Then 30 μl of 5 *N* NaOH and 0.3 ml of water were added in succession. The resulting solution was heated for 15 min at 95 °C. During that time the ethanol evaporated and an essentially aqueous solution of the hydrolyzed ligand was present. Then a reducing agent and 30 mCi or less of Tc-99m in generator pertechnetate saline (0.5 ml or less) were added. After leaving a short period at room temperature—or heating at 95 °C for an additional 15 min, depending on the reducing agent used—the pH was adjusted to about 8. Reducing agents and amounts were: 0.5 mg of freshly dissolved sodium dithionite, 0.010 mg of 0.22 micron-filtered formamidine sulfinic acid, or levels of 0.0022(7) and 0.10 mg stannous chloride dihydrate.

The product mixture was purified by preparative HPLC, using a 25-cm octadecylsilane (ODS) column‡ and eluting with 0.01 *M* sodium phosphate (pH 6) and acetonitrile with a gradient of 5-30% acetonitrile; time 10 min with a flow rate of 1.7 ml/min. The preparations were analyzed for reduced hydrolyzed technetium on silica gel thin-layer strips. Both main components had R_f values of 1 in 0.9% NaCl.

Studies of protein binding were carried out in plasma using an ultrafiltration method previously described (*3*).

Animal studies, general. Organ biodistribution and acute toxicity studies were carried out in mice; blood disappearance and bile appearance rates were determined by sampling of blood or bile in rats; and renal excretion rates of Tc-DTPA, OIH, and the two Tc-CO_2-DADS components were determined in rabbits because of greater ease of urine sampling. The HPLC-purified Tc-CO_2-DADS components were used directly except for dilution as necessary. In general, HPLC collected volumes were 1-1.5 ml and were not diluted for rabbit studies; were diluted two- to tenfold for rat studies; and were diluted about twentyfold for mouse studies. In most cases determinations were made with simultaneous administration of OIH.

Biodistribution. The time course of organ distribution was determined in groups of six Hal Cr female albino mice. Each was injected with 0.10 ml (0.5 μCi) of the preparation. For comparison purposes, 0.2 μCi OIH was added to each injection. The mice were placed in metabolic cages for the collection of excreted urine. At indicated intervals after injection, the urethra was ligated and the mice killed with chloroform vapor. The organs were removed and counted in a dual-channel counter with correction for I-131 crossover into the Tc-99m channel.

Blood disappearance rates and biliary excretion. These determinations were made in male Sprague-Dawley rats. For blood studies the animals were anesthetized with sodium pentobarbital, a catheter was placed in a femoral vein for tracer injections and hydration, and another was placed in a carotid artery for blood sampling. About 20

μCi (0.25 ml) each of OIH and the Tc-99m complex under study was injected, and 0.1- to 0.2-ml samples of blood were taken at 1, 2, 3, 4, 5, 6, 9, 12, 15, 20, 25, 30, 45, 60, 75, and 90 min after injection. Biliary excretion in the absence of renal function was determined by cannulating the common bile duct, ligating the renal pedicles, and collecting bile in 4-min fractions for 90 min.

Renal excretion. The rate of renal excretion was measured in New Zealand albino male rabbits. They were anesthetized with ketamine and xylazine and placed on a gamma camera provided with digital storage. After injection of 0.5–1 mCi of the Tc-99m complex containing 0.5 μCi of OIH, images were collected on tape for 45 min. At 35 min after injection, urine was expelled from the bladder and the percentage of injected dose contained in the expelled urine was determined. Accumulation of bladder radioactivity was monitored by placing a region of interest over the bladder image. The drop in the radioactivity in the bladder after expelling the urine sample (50–80% of the bladder radioactivity) allowed construction of the bladder time-activity curve in terms of percent injected dose (*3*). OIH excretion was based on the change in bladder Tc-99m radioactivity and the amount of I-131 in the urine sample. These values were compared with studies made with OIH alone, in which 250 μCi were injected and the bladder radioactivity monitored for I-131.

Studies of tubular transport inhibition. The effect of probenicid as an inhibitor of renal tubular transport (*8*) on the excretion and organ distribution of Tc-CO_2-DADS-A was studied in mice as described (*4,5*). A dose of 50 mg/kg of probenicid was given 10 min before injection of radiochemicals. OIH was injected simultaneously. The values at 10 min were determined because they have been found to be kinetically representative.

Toxicity. Acute toxicity studies were performed in 52 Hal Cr female mice. The formulation was carried out with added ethanol, NaOH, and HCl, and with the heating steps described. The doses administered ranged from 200 to 500 mg/kg.

RESULTS

Synthesis. The chelating-agent precursor, ethyl N,N′-bis(benzoylmercaptoacetyl)-2,3-diaminopropanoate (ethyl bis-benzoyl-CO_2-DADS) was synthesized from 2,3-diaminopropanoic acid as shown in Fig. 1. The route involved formation of the chloroacetamide as an intermediate that is efficiently alkylated by thiobenzoate to give the final product. The ethyl ester and thiobenzoyl groups were removed by hydrolysis at high pH during the initial heating period. That hydrolysis of the ethyl ester is complete was supported by the lack of ethyl-group protons in the PMR spectrum of an isolated sample; moreover, the same Tc-99m radiochemical

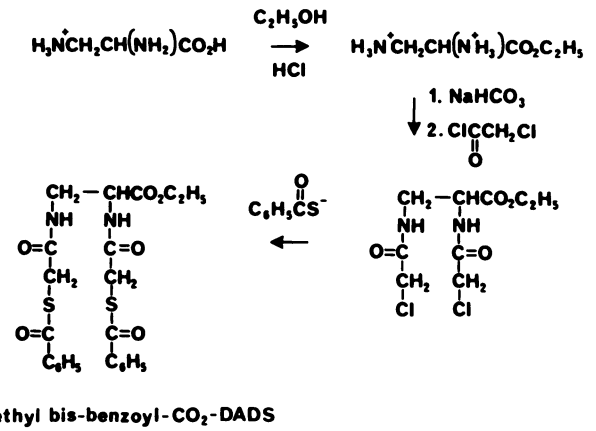


FIG. 1. Synthesis of ethyl N,N′-bis(benzoylmercaptoacetyl)-2,3-diaminopropanoate (bis-benzoyl-CO_2-DADS), the sulfhydryl-protected precursor of the chelating agent N,N′-bis(mercaptoacetyl)-2,3-diaminopropanoate.

components are observed in HPLC chromatograms from either the ethyl or the methyl ester chelating-agent precursors. Several reducing agents and conditions were evaluated to determine optimum conditions for Tc-99m complex formation.

In vitro studies. Analysis of a typical Tc-CO_2-DADS preparation by high-performance liquid chromatography is shown in Fig. 2. Two major components have been present, in varying ratios, in every preparation. The first peak, Tc-CO_2-DADS-A, represents the component with superior biological properties. Heating at 95 °C for 30 min without added reducing agent resulted in less than 10% of both components, in a ratio similar to that shown. The use of stannous ion at room temperature gave the two components shown in about 65% yield, with a small early component (5%) and a larger one (30%) with a longer retention time. Heating the mixture immediately after the addition of stannous ion did not change the A:B ratio. However, the ratio of the main components was about 1:1. The use of dithionite at room temperature resulted in over 90% A and B, although in a 2:3 ratio. Formamidine sulfinate at levels of 20 μg, with heating

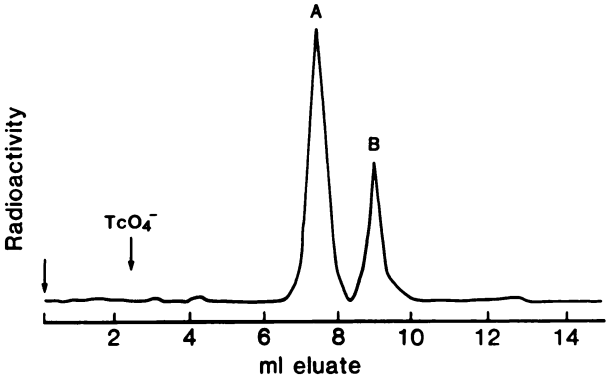


FIG. 2. High-performance liquid chromatogram of Tc-CO_2-DADS preparation. Conditions are given in experimental section. Components referred to as A and B in text are indicated.

for 15 min at 95 °C, gave over 95% A and B, but in about a 7:3 (A:B) ratio. This result was shown to be independent of these reducing agents, since the same result was observed with dithionite when the preparation was heated after addition of reducing agent, but before neutralization.

For animal studies the radioactivity corresponding to HPLC peaks A and B was collected. The chemical stability of the isolated material is high since no change was observed with time, dilution, or treatment with NaOH or HCl and heating at 95 °C for 30 min.

At 10 min, duplicate determinations of binding to plasma proteins resulted in 93% (range 93-94) of Tc-CO_2-DADS-A bound, and at 30 min 94% (94-94) bound. Simultaneously determined OIH was 64% (61-67) bound at 10 min, and at 30 min 56% (55-57), in agreement with previous findings (*3*). The bound fractions of Tc-CO_2-DADS-B were 87% (82-91) at 10 min and 90% (89-92) at 30 min. These values are similar to the high protein binding (95%) found for Tc-DADS (*3*).

In vivo studies. As in our earlier study of Tc-DADS, the results in different species showed good qualitative and, in the case of renal excretion, quantitative agreement. No reaction was noted to the small doses of acetonitrile resulting from HPLC elution of the radiochemicals at about 15% acetonitrile, and the OIH values from simultaneous administration were in good agreement with earlier findings (*3*).

Organ biodistribution. Table 1 shows the organ distribution in mice of Tc-CO_2-DADS-A from 5 min to 2 hr after injection, and of Tc-CO_2-DADS-B at 10 min and 2 hr for comparison. Over the first 15 min, Component A equals or slightly exceeds OIH in renal excretion. Blood disappearance was rapid, with 0.6% remaining in the blood at 30 min. The initial liver radioactivity (~8% at 5 min) appeared to return to the blood, since 1.6% or less was seen in the intestine at any time interval, and less than 1% was in the liver at 2 hr. The kidneys, with 5.6% of the dose at 5 min, contained less than the 12.6% found for Tc-DADS at 5 min. Since 45% of Tc-CO_2-DADS-A was already in the urine at 5 min, compared with 28% of Tc-DADS, it appears that the peak kidney radioactivity occurs less than 5 min after injection. Retention in the kidneys was low, with less than 1% of the dose remaining in them by 30 min. That Tc-CO_2-DADS-B was more slowly cleared is shown by lower levels in the urine at 10 min. The higher liver radioactivity seems to account for this. At 2 hr the liver has cleared and renal excretion was only slightly lower than that of OIH determined simultaneously. Negligible biliary excretion is also seen with Tc-CO_2-DADS-B.

Blood disappearance. Comparative blood disappearance curves in rats for both A and B components, OIH, and Tc-DTPA, are shown in Fig. 3. OIH showed the most rapid disappearance through 75 min. However, Tc-CO_2-DADS-A, with a higher initial value, resulted in comparable curve slopes. The high values in the 1- to

TABLE 1. BIODISTRIBUTION DATA OF Tc-CO_2-DADS-A AND Tc-CO_2-DADS-B IN MICE WITH CORRESPONDING OIH URINE PERCENTAGES*

				Tc-CO_2-DADS-A			OIH
Time	Blood	Liver	Kidneys	Stomach	Intestines	Urine	Urine
5 min	8.19 ±0.51	7.81 ±0.43	5.61 ±0.67	0.24 ±0.02	1.61 ±0.18	45.52 ±2.16	42.02 ±6.45
10 min	3.10 ±0.19	4.26 ±0.32	2.23 ±0.31	0.11 ±0.004	0.82 ±0.05	67.97 ±0.97	64.94 ±0.89
15 min	1.95 ±0.21	3.79 ±0.46	1.30 ±0.10	0.09 ±0.02	0.86 ±0.16	75.08 ±2.06	78.24 ±0.46
30 min	0.59 ±0.05	1.34 ±0.13	0.51 ±0.05	0.07 ±0.01	1.05 ±0.12	80.82 ±1.31	
120 min	0.21 ±0.04	0.78 ±0.20	0.25 ±0.05	0.04 ±0.01	1.46 ±0.19	86.57 ±0.92	82.43 ±0.95
				Tc-CO_2-DADS-B			
10 min	3.64 ±0.32	14.83 ±1.33	2.87 ±0.33	0.13 ±0.02	1.00 ±0.10	51.94 ±2.31	
120 min	0.14 ±0.01	3.71 ±0.43	0.14 ±0.03	0.02 ±0.002	0.21 ±0.01	79.16 ±1.09	

* Values are percent injected dose, mean and s.e.m., for six mice at each time after injection.

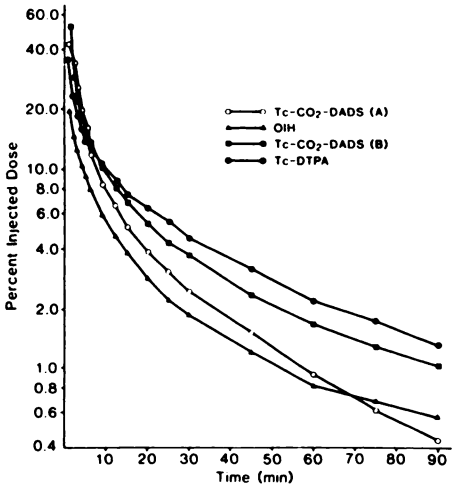


FIG. 3. Blood disappearance curves for Tc-CO_2-DADS components A and B in rats, with reference radiopharmaceuticals OIH and Tc-DTPA. Data are plotted as means for five or more animals at each sampling time.

5-min period following injection may be due to a smaller initial volume of distribution because of marked protein binding. For comparison purposes the Tc-CO_2-DADS-A radioactivity remaining in the blood was 5% at 16.5 min and 2% at 36 min, while corresponding values for Tc-DADS were 5% at 19 min and 2% at 68 min. The disappearance of Tc-CO_2-DADS-B was significantly faster ($p < 0.05$) than with Tc-DTPA, an indicator of glomerular filtration rate (*9*), and significantly slower than with Tc-CO_2-DADS-A.

Renal excretion. Comparative rates of renal appearance are shown in Fig. 4. From 10 min to 35 min, Tc-CO_2-DADS-A was found in the urine slightly more than OIH, although differences were significant only at 35 min ($p < 0.05$). In contrast, Tc-CO_2-DADS-B was significantly lower at early times but was similar to Component A and OIH by 35 min. These results suggest a similar degree of overall specificity, but different renal handling kinetics among these compounds. All were found in the urine in amounts exceeding Tc-DTPA over the 35-min period measured.

Tubular transport inhibition. Clinical studies with Tc-DADS indicate that decreased renal function reduced renal excretion of Tc-DADS to a greater extent than OIH (*6*). Experiments with probenicid as an inhibitor of tubular secretion demonstrated a decrease in renal excretion of Tc-DADS to a much greater extent than with OIH (*4,5*). Since these results appear to be consistent and suggest that the effect of probenicid may be an indicator of renal excretion efficiency in patients with reduced renal function, we also studied Tc-CO_2-DADS-A under these conditions. The results indicate that its decrease in renal excretion is much less than for Tc-DADS, but still greater than for OIH (Table 2). Biliary excretion was not increased significantly for Component A, but liver radioactivity was.

Biliary excretion. Biliary excretion of radioactivity in the absence of renal function was slow, amounting to 3.1% (range 2.4–3.6) in 90 min; this contrasts with 19% for Tc-DADS in the same time. At 90 min measurement of Tc-99m-DADS-A radioactivity in other organs was 1% in the kidneys, 21% in the blood, 4% in the liver, 0.1% in the spleen, 0.3% in the stomach, and 22% in muscle. Similarly determined biliary excretion of OIH was 5.9% (range 4.2–8.7%) at 90 min.

Acute toxicity. Acute toxicity studies resulted in no deaths over 48 hr with doses up to 500 mg/kg, and little or no reaction was observed on injection.

DISCUSSION

Clinical evaluation of Tc-DADS in a limited number of renal-transplant patients (*6*) demonstrated high kidney-to-background ratios (similar to those of OIH) and thus high extraction efficiencies in patients with good renal function, but poor ratios (much lower than with OIH) in patients with moderate to severe decreases in renal function. Moreover, in patients with renal impairment, hepatobiliary excretion became significant. An unanticipated finding was that the high degree of protein binding of Tc-DADS confined radioactivity to the vascular system rather than to the extracellular space as with Tc-DTPA, and increased the ease of placing well-defined regions of interest on major vessels. This facilitates quantitative analysis of renal function.

The biological results of the studies with Tc-CO_2-DADS-A indicate that this component has significantly improved parameters for evaluation of renal function relative to Tc-DADS. In animals with normal renal function, the rate of renal excretion is equivalent to that of OIH and the specificity for renal excretion is nearly

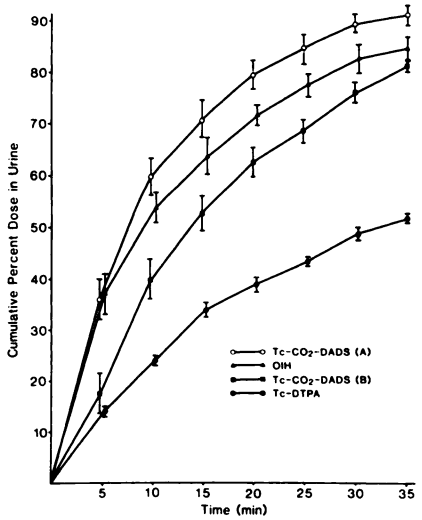


FIG. 4. Renal excretion of Tc-CO_2-DADS components A and B in rats, with reference radiopharmaceuticals OIH and Tc-DTPA for comparison. Data are mean and range for three studies at each point.

TABLE 2. EFFECT OF PROBENICID ON BIODISTRIBUTION OF RENAL AGENTS*

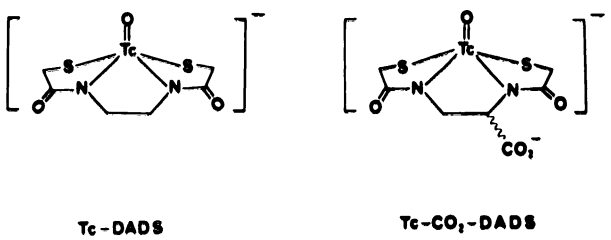
Organ	Tc-DADS		Tc-CO_2-DADS-A		OIH	
	Control	Treated	Control	Treated	Control	Treated
Blood	1.85 ±0.37	19.53 ±0.69	3.37 ±0.16	10.20 ±0.81	4.58 ±0.24	7.49 ±0.41
Kidneys	4.25 ±1.16	2.69 ±0.05	2.53 ±0.24	3.93 ±0.19	2.83 ±0.38	3.79 ±0.18
Liver	2.24 ±0.26	17.13 ±1.69	4.21 ±0.24	14.36 ±0.59	1.31 ±0.10	2.68 ±0.19
Intestines	4.69 ±0.35	12.78 ±0.91	0.77 ±0.03	1.83 ±0.09	1.12 ±0.11	2.18 ±0.13
Urine	60.90 ±2.34	10.69 ±1.18	67.14 ±0.73	38.68 ±2.47	64.94 ±0.89	52.62 ±2.53

* Values are percent injected dose at 10 min after injection, mean and s.e.m., for six or more mice with each agent. Probenicid at a dose of 50 mg/kg was given 10 min before injection of radiopharmaceuticals.

complete. The only indication of biological inferiority to OIH is lower renal excretion than for OIH in mice pretreated with probenicid as an inhibitor of renal tubular transport. However, the depression of renal excretion by probenicid treatment was from 68% to 39% at 10 min, a decrease of 43%, whereas Tc-DADS showed a depression from 61% to 11%, a decrease of 82% under the same conditions. The depression of OIH was from 65% to 52%, or a 20% decrease. The actual decrease in tubular secretion of OIH was probably closer to that of Tc-CO_2-DADS-A, since the former's lower degree of protein binding allows excretion by glomerular filtration. Glomerular filtration of Tc-CO_2-DADS-A is probably insignificant owing to its marked protein binding. These factors could be sorted out if the degree of protein binding of each were known under the conditions of probenicid treatment. Biliary excretion in the absence of renal function amounted to less than 3% in 90 min, in contrast to 19% for Tc-DADS. Biliary excretion of OIH was 5.9% and thus was similar in magnitude. These improvements have been demonstrated without the loss of a high degree of plasma-protein binding.

The obstacle to easy clinical availability of Tc-CO_2-DADS-A lies in the HPLC purification step. Our working hypothesis is that the two major components in the Tc-CO_2-DADS preparations are a result of chelate-ring isomers, as indicated in Fig. 5. Alternative binding of a carboxylate group in place of an amide group seems unlikely, since a less stable series of 5, 6, and 8 members of chelate rings would result. In support of this hypothesis are the observations that (a) heating for 1 min or less after addition of the reducing agent results in only Tc-CO_2-DADS-B, (b) reduction with dithionite and no heating favors Tc-CO_2-DADS-B, whereas heating favors Tc-CO_2-DADS-A, and (c) the analog prepared from 3,4-diaminobenzoic acid, in which the carboxylate group must lie in the plane of the chelate-ring carbon atoms, gives only one component. Work is under way to prepare long-lived Tc-99 complexes of Tc-CO_2-DADS, separate them, and evaluate their structures with mass spectrometry (*2*) and potentially with crystallography. Knowledge of the structures involved will aid in the understanding of how these complexes are handled by the renal tubular system in a manner that essentially differs only in kinetics.

The high specificity of both components of Tc-CO_2-DADS suggests that small amounts of Component B may not seriously impair the potential efficacy of the preparation. Thus, work is continuing to optimize the yield of the A component of Tc-CO_2-DADS. Under study are parameters such as temperature (since some control due to heating has already been observed), solvent, and use of other technetium complexes as intermediates. Alternatively it may be possible to modify the chelating agent so that isomers are not produced while renal excretion kinetics and specificity are maintained.



Tc-DADS Tc-CO_2-DADS

FIG. 5. Structure of Tc-N,N'-bis(mercaptoacetyl)ethylenediamine (Tc-DADS) as described by Davison and co-workers (*1,2*), and expected structure of Tc-N,N'-bis(mercaptoacetyl)-2,3-diaminopropanoate (Tc-CO_2-DADS) described in this study. Carboxylate group may be either *syn* or *anti* to oxotechnetium bond and is thus indicated by a wavy line.

Although there is still room for improvement, these results suggest that Tc-CO_2-DADS-A would be a useful alternative to both Tc-DTPA and OIH for the evaluation of renal function.

FOOTNOTES

* Galbraith Laboratories, Inc., Knoxville, TN.

† Varian EM 360A PMR spectrometer.

‡ Altex Model 312 gradient liquid chromatograph with variable wavelength spectrometer and sodium iodide crystal scintillation detectors for mass and radioactivity detection. Column used was 4.6 × 250 mm ODS ultrasphere, 5 micron from Altex/Beckman.

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