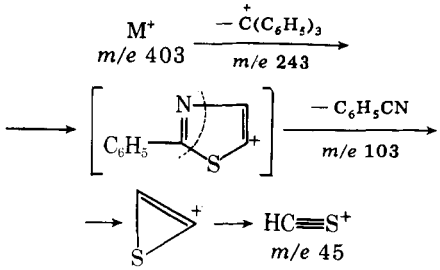

Scheme V

in thiazole derivatives with electron-withdrawing groups on C-5 or C-2 (36). The two peaks at *m/e* 77 and 51 can be attributed to the $C_6H_5^+$ and $C_4H_3^+$ radical ions.

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Improved Synthesis of *N*-(2,6-Dimethylphenylcarbamoylmethyl)iminodiacetic Acid and Analogs

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Abstract □ A new synthesis of *N*-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid directly from nitrilotriacetic acid was developed. Six analogs also were synthesized. Their technetium Tc 99m complexes were prepared and characterized. Electrophoresis and chromatography were used to determine the radiochemical purity of each complex.

Keyphrases □ *N*-(2,6-Dimethylphenylcarbamoylmethyl)iminodiacetic acid—and analogs, synthesized, ^{99m}Tc-complexes prepared □ Technetium Tc 99m complexes—various substituted iminodiacetic acids prepared □ Iminodiacetic acids, substituted—synthesized, ^{99m}Tc-complexes prepared □ Radiopharmaceuticals, potential—^{99m}Tc-complexes of various substituted iminodiacetic acids prepared

In recent years, considerable attention has been given to the development of new γ-emitting radiopharmaceuticals for the evaluation of the hepatobiliary function. Currently, the only commercially available agent of this type is rose bengal sodium I 131 (1). The relatively poor physical characteristics of iodine-131 have hindered the widespread use of this radiopharmaceutical.

DISCUSSION

Because of the nearly ideal physical properties of technetium Tc 99m and its widespread availability in most nuclear medicine laboratories,

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a search has been underway to develop ^{99m}Tc-labeled hepatobiliary radiopharmaceuticals. ^{99m}Tc-Complexes of the following ligands have been suggested for the evaluation of hepatobiliary function: dihydrothioctic acid (2), mercaptoisobutyric acid (3), penicillamine (4), tetracycline (5), pyridoxylideneglutamate (6, 7), and *N*-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid (I) (8). The most promising of these hepatobiliary radiopharmaceuticals appears to be the ^{99m}Tc-complex of I.

Callery *et al.* (9) first prepared I as a lidocaine analog with an iminodiacetic acid functional group capable of forming a stable complex with ^{99m}Tc. The rapid and extensive biliary excretion of ^{99m}Tc-I after intravenous injection into mice led to intensive investigation of this complex as a potential hepatobiliary radiopharmaceutical. The original synthesis of I required 48 hr and involved treatment of 2,6-xylidine with chloroacetyl chloride to form 2-chloro-2′,6′-dimethylacetanilide. Nucleophilic displacement of the chloride ion by the nitrogen of iminodiacetic acid gave I in an overall yield of 20%.

As part of a study relating molecular structure to biliary excretion of ^{99m}Tc-radiopharmaceuticals (10), a new one-step synthesis of I was developed. The synthesis involves reaction of a pyridine solution of nitrilotriacetic acid monoanhydride (generated *in situ* by treatment of nitrilotriacetic acid with acetic anhydride in anhydrous pyridine) with 2,6-xylidine for 1 hr at 100°. By using this synthesis, I was obtained in a 69% yield with a total working time of less than 4 hr.

A series of analogs of I (II–VII, Table I) subsequently was prepared by substituting the appropriate amine for 2,6-xylidine. These analogs were prepared both to find a better hepatobiliary agent and to aid in studies of the chemistry and nature of ^{99m}Tc-I.

The ^{99m}Tc-complexes of these compounds were prepared by stannous chloride reduction of pertechnetate ion ($^{99m}TcO_4^-$) in an aqueous solution of the appropriate compound. Electrophoresis was used to evaluate the radiochemical purity of each complex. The two most common radiochemical impurities encountered in ^{99m}Tc-radiopharmaceuticals are unreduced pertechnetate ion and reduced hydrolyzed technetium (TcO_2). Electrophoresis easily separated these two impurities from most complexes. Since ^{99m}Tc-IX migrates the same distance on electrophoresis as TcO_4^-, chromatography (silica gel–acetone) was used to evaluate purity in this case.

On this chromatographic system, the complex remained at the origin while pertechnetate migrated with the solvent front. In all cases, a radiochemical purity of at least 98% was obtained. The stabilities of the complexes were evaluated by serial electrophoreses. No significant decomposition was detected for at least 4 hr after preparation. Animal biodistribution studies on the ^{99m}Tc-complexes are currently in progress and will be reported elsewhere.

^{99m}Tc-VII, which appears to have a higher uptake in the GI tract of mice than ^{99m}Tc-I, may prove to be a useful hepatobiliary agent.

EXPERIMENTAL[1]

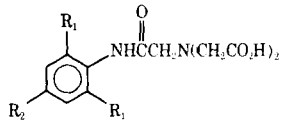
***N*-(2,6-Dimethylphenylcarbamoylmethyl)iminodiacetic Acid (I)**—*Method A*—A suspension of nitrilotriacetic acid (5.0 g, 26 mmoles) in 40 ml of anhydrous pyridine was placed in a three-necked round-bottom flask equipped with a nitrogen inlet tube, a condensor, a calcium sulfate drying tube, and a thermometer. After flushing with nitrogen, the suspension was heated at 50° for 10 min, at which time most of the nitrilotriacetic acid had dissolved. Acetic anhydride (3.25 g, 31 mmoles) was added, and the solution was heated at 100° for 30 min. After cooling to 50°, 2,6-dimethylaniline was added and the solution was again heated at 100° for 1 hr.

Evaporation of the pyridine *in vacuo* left a yellow oil, which was dissolved in a minimal amount of aqueous ammonia. The solution was extracted three times with an equal volume of ether and then treated with decolorizing carbon[2]. After filtering, the near colorless solution was acidified to pH 3, resulting in formation of a white precipitate. Recrystallization from ethanol–water yielded 3.0 g (39.2%) of white needles, mp 211–213°; IR (mineral oil): 3310 (NH) and 1660–1720 (broad, acid and amide C=O) cm^{-1}; PMR (dimethyl sulfoxide-d_6): δ 2.14 (s, 6H, Ar-CH_3), 3.50 (s, 2H, $NCOCH_2N$), 3.58 (s, 4H, NCH_2CO), and 7.04 (s, 3H, Ar-H) ppm.

[1] Proton magnetic resonance (PMR) spectra were obtained on a Perkin-Elmer Hitachi R12A spectrometer with chemical shifts reported relative to tetramethylsilane. IR spectra were obtained on a Pye-Unicam SP1000 spectrophotometer. Melting points were determined in a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Robertson Microanalytical Laboratory, Florham Park, N.J.

[2] Norit, Fisher Scientific, Fair Lawn, N.J.

Table I—Synthetic Analogs of *N*-(2,6-Dimethylphenylcarbamoylmethyl)iminodiacetic Acid



Compound	R_1	R_2	Yield, %	Technetium Complexes: Electrophoresis, R_s[a]	Technetium Complexes: Chromatography, R_f
I	CH_3	H	69	0.68	0
II	H	H	61	0.68	0
III	H	CH_3	50	0.66	0
IV	CH_3	Br	48	0.65	0
V	H	NO_2	31	0.66	0
VI	H	COOH	70	0.98	0
VII	H	I	62	0.65	0
TcO_2				0	0
TcO_4^-				1	1

[a] See *Experimental* for explanation.

Anal.—Calc. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.19; H, 6.19; N, 9.50.

Method B—This method was the same as Method A, except that the molar ratio of acetic anhydride to nitrilotriacetic acid was increased from 1.2:1 to 1.5:1. Reaction of nitrilotriacetic acid (5.0 g, 26 mmoles), acetic anhydride (3.98 g, 39 mmoles), and 2,6-dimethylaniline yielded (after recrystallization) 5.24 g (69%) of I.

***N*-(Phenylcarbamoylmethyl)iminodiacetic Acid (II)**—Compound II was prepared by Method A from nitrilotriacetic acid (5.0 g, 26 mmoles), acetic anhydride (3.25 g, 31 mmoles), and aniline (2.42 g, 26 mmoles). After recrystallization from ethanol–water, 4.25 g (61%) of II was obtained, mp 153° dec.; IR (mineral oil): 3370 (NH) and 1670–1720 (broad, acid and amide C=O) cm^{-1}; PMR (dimethyl sulfoxide-d_6): δ 3.50 (s, 2H, NCH_2CON), 3.58 (s, 4H, NCH_2CO_2), and 7.4 (multiplet, 5H, Ar-H) ppm.

Anal.—Calc. for $C_{12}H_{14}N_2O_5 \cdot H_2O$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.35; H, 5.72; N, 9.92.

***N*-(4-Methylphenylcarbamoylmethyl)iminodiacetic Acid (III)**—Reaction of nitrilotriacetic acid (15.29 g, 0.08 mole), acetic anhydride (12.25 g, 0.12 mole), and *p*-toluidine (8.57 g, 0.08 mole) (Method B) gave III. Recrystallization from ethanol–water yielded 11.1 g (49.6%) of white crystalline III, mp 205.5–206°; IR (mineral oil): 3300 (NH) and 1720 and 1690 (C=O) cm^{-1}; PMR (dimethyl sulfoxide-d_6): δ 2.23 (s, 3H, $ArCH_3$), 3.45 (s, 2H, $NCOCH_2N$), 3.53 (s, 4H, NCH_2CO_2), 7.10 (d, 2H, Ar-H), and 7.45 (d, 2H, Ar-H) ppm.

Anal.—Calc. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.95; H, 5.55; N, 10.29.

***N*-(4-Bromo-2,6-dimethylphenylcarbamoylmethyl)iminodiacetic Acid (IV)**—Reaction of nitrilotriacetic acid (4.47 g, 0.023 mole), acetic anhydride (3.58 g, 0.035 mole), and 4-bromo-2,6-dimethylaniline hydrobromide (5.53 g, 0.023 mole) (Method B) yielded (after recrystallization from ethanol–water) 4.16 g (47.7%) of IV, mp 198–199° dec.; IR (mineral oil): 3310 (NH) and 1680–1720 (broad, acid and amide C=O) cm^{-1}; PMR: δ 2.22 (s, 6H, $ArCH_3$), 3.36 (s, 2H, NCH_2CON), 3.49 (s, 4H, NCH_2CO_2), and 7.23 (s, 2H, Ar-H) ppm.

Anal.—Calc. for $C_{14}H_{17}BrN_2O_5 \cdot H_2O$: C, 42.98; H, 4.89; N, 7.16. Found: C, 42.90; H, 4.56; N, 7.24.

***N*-(4-Nitrophenylcarbamoylmethyl)iminodiacetic Acid (V)**—Reaction of nitrilotriacetic acid (15.0 g, 0.078 mole), acetic anhydride (11.94 g, 0.117 mole), and 4-nitroaniline (10.77 g, 0.078 mole) (Method B) followed by recrystallization from ethanol–water resulted in formation of 7.49 g (31%) of V, mp 250° dec.; IR (mineral oil): 3200 (NH) and 1690 and 1720 (C=O) cm^{-1}; NMR: δ 3.58 (s, 6H, NCH_2CO), 7.88 (d, 2H, Ar-H), and 8.22 (d, 2H, Ar-H) ppm.

Anal.—Calc. for $C_{12}H_{13}N_3O_7$: C, 46.31; H, 4.21; N, 13.50. Found: C, 46.04; H, 4.50; N, 13.50.

***N*-(4-Carboxyphenylcarbamoylmethyl)iminodiacetic Acid (VI)**—Reaction of nitrilotriacetic acid (5.0 g, 26 mmoles) and acetic anhydride (3.25 g, 26 mmoles) (Method A) gave (after recrystallization from ethanol–water) 5.67 g (70.3%) of VI, mp 227–229°; IR (mineral oil): 3350 (weak, NH) and 1690 (acid and amide C=O) cm^{-1}; PMR (dimethyl sulfoxide-d_6): δ 3.58 (s, 6H, NCH_2CO), 7.73 (d, 2H, Ar-H), and 7.97 (d, 2H, Ar-H) ppm.

Anal.—Calc. for $C_{13}H_{14}N_2O_7 \cdot H_2O$: C, 48.90; H, 4.74; N, 8.78. Found: C, 48.80; H, 4.65; N, 8.61.

***N*-(4-Iodophenylcarbamoylmethyl)iminodiacetic Acid (VII)**—Compound VII was obtained from nitrilotriacetic acid (4.47 g, 0.023 mole), acetic anhydride (3.58 g, 0.035 mole), and 4-iodoaniline (5.12 g, 0.023 mole) (Method B). Recrystallization from 80% aqueous ethanol yielded white crystals, 5.62 g (62%), mp 194° dec.; IR (mineral oil): 3300 (NH) and 1710 and 1675 (C=O) cm^{-1}; PMR (dimethyl sulfoxide-d_6): δ 3.51 (s, 2H, NCH_2CON), 3.55 (s, 4H, NCH_2CO_2), 7.48 (d, 2H, Ar-H), and 7.60 (d, 2H, Ar-H) ppm.

Anal.—Calc. for $C_{12}H_{13}IN_2O_5$: C, 36.75; H, 3.34; N, 7.14. Found: C, 36.73; H, 3.51; N, 7.25.

Preparation of ^{99m}Tc-Complexes—A solution of 10 mg of compound in 0.5 ml of 0.1 *N* NaOH was prepared, and the pH was adjusted to 5–5.5 with 0.05 *N* HCl. After addition of 0.3 ml of generator eluate (obtained by saline elution of a 500-mCi ^{99}Mo–^{99m}Tc generator[3] at a specific concentration of 10–20 mCi/ml), the solution was purged with nitrogen for 5 min, and 0.1 ml of freshly prepared stannous chloride dihydrate solution (250 μg/ml in 0.001 *N* HCl) was then added. The solution was kept at room temperature for 20 min prior to use.

Electrophoresis and Chromatography[4]—Electrophoresis was performed on paper[5] at constant voltage (600 v, 30 min) with a 0.01 *M* sodium bicarbonate buffer (pH 7). Under these conditions, $^{99m}TcO_4^-$ migrated approximately 13 cm. A pertechnetate standard was utilized with all samples. The distance each complex migrated was determined by scanning the dried paper with a chromatogram scanner equipped with a 2.54-cm sodium iodide detector and a collimator, which consisted of 0.635 cm of lead with a 2.54-cm × 30-mm slit. The results obtained on any given electrophoragram were expressed as the following ratio:

$$R_s = \frac{\text{distance migrated by complex}}{\text{distance migrated by } ^{99m}TcO_4^-} \quad \text{(Eq. 1)}$$

These R_s values were essentially independent of the distance migrated by the pertechnetate ion over a range of at least 11–15 cm.

[3] E. R. Squibb & Sons, Princeton, N.J.

[4] Chromatography was performed on Eastman 13181 silica gel eluted with acetone.

[5] Whatman 3MM.

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Dissolution Profiles of Drugs from Tablets

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Received January 3, 1977, from the *Pharmaceutical Research Laboratories, Central Research Division, Takeda Chemical Industries, Ltd., Yodogawa-ku, Osaka, 532, Japan.* Accepted for publication February 15, 1978.

Abstract □ A theoretical equation to describe the drug dissolution from a tablet was derived by combining an equation for the disintegration rate of a tablet with an equation for the dissolution of particles. The theory is based on the assumptions that: (*a*) dissolution occurs only from the particles released in a medium by tablet disintegration, (*b*) the number of particles released into a medium obeys the equation $N = N_0(T/T_d)^m$, and (*c*) the dissolution of particles, which are spherical in shape, is represented by the equation previously given by Brooke. Tablet dissolution *versus* time plots, obtained by calculating the equation with a computer, gave an S-shaped curve between the dissolution curve for particles starting at time zero and the curve for particles starting at the tablet disintegration time. The joint influences of disintegration and particle dissolution on the overall tablet dissolution profile also were examined. When dissolution of powders was rapid, disintegration of a tablet directly influenced its dissolution. When powders intrinsically dissolved slowly, the effect of disintegration on the tablet dissolution profile was slight.

Keyphrases □ Dissolution, tablet—theoretical equation derived, effects of tablet disintegration and particle dissolution □ Disintegration, tablet—effects on dissolution, theoretical equation derived □ Tablet dissolution—theoretical equation derived, effects of tablet disintegration and particle dissolution

The dissolution rate of a drug from its solid dosage forms is important relative to bioavailability since dissolution is usually the rate-limiting process in the absorption of poorly soluble drugs.

The overall dissolution profiles for solid dosage forms can be obtained from dissolution tests (1–3). The dissolution data obtained may involve factors related to the drug dissolution rate, the drug particle size (distribution), and the disintegration rate of the dosage forms. The effect of these factors on the dissolution profiles is so complex that no satisfactory quantitative evaluation of the dissolution properties of solid dosage forms is obtained from a measured dissolution profile.

Attempts to describe dissolution profiles include empirical functions that enable representation of the actual results with a minimum number of parameters (4–8). However, the values of the parameters of the distribution function employed give no useful information about the improvement of tablet dissolution.

Theoretical considerations of powder dissolution in relation to particle-size distribution were first attempted by Higuchi and coworkers (9, 10). A more exact equation then was developed that permits calculation of the dissolution profiles of log-normal powders with or without a computer (11–13). Later, a simple relationship was found between the tablet disintegration rate and time (14).

To evaluate tablet dissolution quantitatively, an equation was derived in the present study by combining an equation for tablet disintegration with an equation for

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