242° (decomp.) (from a mixture of methanol and ethanol). Ninhydrin reaction : blue. Yield, 0.68 g. (52%). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2 \cdot H_2O$: C, 60.42; H, 6.52; N, 10.07. Found : C, 60.58; H, 6.66; N, 10.09.

N-(2,4-Dinitrophenyl) derivative (Vc) : Yellow granules (from ethanol), m.p. 252° (decomp.). *Anal.* Calcd. for $C_{20}H_{18}O_7N_4$: C, 56.33; H, 4.26. Found : C, 56.49; H, 4.54.

Methyl ester hydrochloride : Slightly yellow granules, m.p. 221° (decomp.) (from a mixture of ethanol and iso-propylether). IR ν_{max}^{Nujol} cm^{-1} : 1760 (ester), 1650 (ring CO). *Anal.* Calcd. for $C_{15}H_{18}O_3N_2 \cdot HCl$: N, 9.01. Found : N, 9.05.

2-(3-Oxobutyl)-1(2*H*)-isoquinolone (VII)——A mixture of 3.48 g. (0.024 mole) of 1(2*H*)-isoquinolone prepared from 1-chloroisoquinoline,[3] 40 ml. of ethanol, 2.10 g. (0.03 mole) of methyl vinyl ketone and 3 drops of freshly prepared a 20% sodium hydroxide solution was refluxed for 2 hr. on a water bath. The reaction mixture was refluxed again with additional 2.10 g. (0.03 mole) of methyl vinyl ketone for 1.5 hr. The reaction mixture was evaporated to dryness under reduced pressure, the residue was extracted with chloroform, and the chloroform layer was extracted with a 5% sodium hydroxide solution twice. After washing with water, the chloroform layer was dried over anhyd. sodium sulfate, and the chloroform was evaporated to dryness. The syrupy residue was extracted with ether, the ether extract was passed through an alumina column, and the column was washed with ether. The combined ether eluant was evaporated to dryness, and the residue (a yellow, viscous liquid) was purified by distillation. Yellow, viscous liquid, b.p.$_3$ 174~178°. IR $\nu_{max}^{Cap.}$ cm^{-1} : 1710 (CO), 1650 (ring CO). Yield, 3.71 g. (72%).

2,4-Dinitrophenylhydrazone : Red, crystalline powder (from methanol), m.p. 212~215° (decomp.). *Anal.* Calcd. for $C_{19}H_{17}O_5N_5$: C, 57.72; H, 4.33; N, 17.72. Found : C, 57.10; H, 4.36; N, 18.03.

The Hydantoin (VIII) derived from 2-(3-Oxobutyl)-1(2*H*)-isoquinolone (VII)——This compound was prepared from Ⅶ by the method similar to that used for the preparation of Ⅳ. Colorless granules (from methanol), m.p. 232~233°. IR ν_{max}^{Nujol} cm^{-1} : 3160, 1760, 1710 (NH and CO of hydantoin) and 1642 (ring CO). Yield, 89%. *Anal.* Calcd. for $C_{15}H_{15}O_3N_3$: C, 63,15; H, 5.30; N, 14.73. Found : C, 62.70; H, 5.17; N, 15.03.

DL-2-Amino-2-methyl-4-(1-oxo-2(2*H*)-isoquinolyl)butyric Acid (IX)——This compound was prepared from the hydantoin by the similar method that used for the preparation of Va in 40% yield. Colorless granules (from a mixture of methanol and ethanol), m.p. 257° (decomp.). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found : C, 64.52; H, 6.02; N, 10.61.

2-(3-Oxobutyl)-1,2-benzisothiazolin-3-one-1,1-dioxide (XI)——A mixture of 18.3 g. (0.1 mole) of benzisothiazolin-3-one-1,1-dioxide, 14.0 g. (0.2 mole) of methyl vinyl ketone, 100 ml. of ethanol and 5 drops of a 20% sodium hydroxide solution was refluxed for 4 hr. The reaction mixture was concentrated under reduced pressure, and the solution was allowed to stand in a refrigerator overnight. The separated crystals were filtered, washed with EtOH, and recrystallized from a mixture of EtOH and H_2O. Colorless prisms, m.p. 122~123°. IR ν_{max}^{Nujol} cm^{-1} : 1730 (ring CO), 1715 (CO). Yield, 24.6 g. (97%). *Anal.* Calcd. for $C_{11}H_{11}O_4NS$: C, 52.11; H, 4.39; N, 5.33. Found : C, 52.62; H, 4.35; N, 5.13.

2,4-Dinitrophenylhydrazone : Orange yellow leaflets, m.p. 188°. IR ν_{max}^{Nujol} cm^{-1} : 1730 (ring CO). *Anal.* Calcd. for $C_{17}H_{15}O_7N_5S$: C, 47.11; H, 3.48. Found : C, 47.05; H, 3.60.

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Hisashi Murata and Masahiro Mori*[1] : Distribution and Excretion of Benhepazone administered to Rats.

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In a previous experiment,[1] various kinds of metabolic products of Benhepazone (1-benzylcycloheptimidazol-2(1*H*)-one) was found in urine after its oral administration to

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1) H. Murata, A. Yasumura : Seikagaku, 37, 461 (1965).

rats. This fact indicates that Benhepazone would easily convert into related compounds in an animal body.

The present communication deals with investigations on the distribution of Benhepazone in various tissues and the excretion in urine and feces. It was found that Benhepazone would be almost completely absorbed, followed by the transformation to the related compounds.

Methods

Material and Analytical Method——Benhepazone was synthesized in this laboratory.[2] Its estimation in biological samples was carried out by fluorometry, by the method previously reported.[3]

Animals——Male albino rats (Wistar strain) weighing 120∼135 g. were used to study the distribution of Benhepazone in various tissues and, for the excretion test, the rats of 150∼200 g. in weight were used. These rats were fasted for about 15 hr. before the experiments.

Benhepazone suspended in tragacanth was administered to rats in a dose of 100 mg./kg. with a stomach tube, and the animals were placed in metabolic cages.

Blood——After decapitating the rats, the blood was collected in a beaker containing 0.1 ml. of heparin solution (1000 U/ml.). One ml. of the heparinized blood to 6 ml. of 0.033*N* HCl, heated for 5 minutes at 100°, and cooled under running tap water. This cooled solution was deproteinized in the usual fashion by adding 3 ml. of 10% metaphosphoric acid and the obtained supernatant fluid was subjected to the Benhepazone assay previously described.[3]

Tissues——From the decapitated rat, tissues were quickly excised, weighed, and frozen when necessary.

Tissues were homogenized in 4 volumes of 0.2*N* HCl in a Potter-Elvehjem type glass homogenizer. Benhepazone was determined with 1 ml. of the homogenate.

Feces——Feces collected from the cages were homogenized in 10∼15 volumes of 0.2*N* HCl in a Waring blender and centrifuged. Benhepazone in this supernatant fluid was estimated.

Urine——The collected urine was filtered through cotton and 1 ml. of the filtrate was assayed by the estimation of Benhepazone.

Results and Discussion

It has been found that Benhepazone, by its oral administration to rats is widely distributed in various tissues. As indicated in Table I, Benhepazone was recovered not only from the liver, kidney, and blood, but also from the brain and muscle.

At 0.5 to 1 hour after the administration, the level of Benhepazone in various tissues reached the maximum which rapidly decreased to a low level after 4 hours. This fact suggested that a large portion of Benhepazone absorbed from the gastrointestinal tract might be rapidly excreted in urine and feces. Investigation on the excretion of Benhepazone was carried out, but only a small amount of Benhepazone was found to be excreted.

Table I. Blood and Tissues Levels[a] of Benhepazone in Rats after Oral Administration (100 mg./kg.)

Period after admin. (hr.)	Blood (μg./ml.)	Brain (μg./g.)	Heart (μg./g.)	Liver (μg./g.)	Kidney (μg./g.)	Muscle[b] (μg./g.)
0.5	12.9 ±2.9	10.3 ±3.4	15.3 ±4.7	38.3 ±12.4	20.2 ±7.2	11.8 ±4.1
1	12.6 ±2.8	11.5 ±5.6	17.2 ±8.6	34.3 ±10.9	21.6 ±9.8	13.6 ±7.1
2	11.3 ±1.3	7.49±1.0	11.1 ±2.7	21.7 ± 4.3	14.4 ±2.6	7.64±2.2
4	2.49±0.53	2.33±0.67	2.49±0.62	6.68± 2.0	4.68±0.92	1.83±0.34
6	2.21±1.3	2.24±0.76	2.43±1.1	6.46± 3.4	3.73±1.4	1.95±0.84

a) Expressed in means ± standard deviation from 8 animals.
b) Femoralis muscle.

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[2] H. Nakao, N. Soma, Y. Sato, G. Sunagawa: This Bulletin, **13**, 473 (1965).

[3] H. Murata, T. Wada: This Bulletin, **15**, 1906 (1967).

in urine and feces. As shown in Table II, approximately 0.5% of Benhepazone administered was excreted in urine during 48 hours, and less than 3% in feces. In addition to this fact, it has been observed that only 0.69% of the dose was detected in the digestive tract 24 hours after the administration. Thus, a large portion of Benhepazone administered could not be recovered.

TABLE II. Excretion[a] of Benhepazone in Urine and Feces of Rats after Oral Administration (100 mg./kg.)

Rat No.	Urine		Feces	
	0～24 hr.	24～48 hr.	0～24 hr.	24～48 hr.
1	0.53	0.038	2.32	0.20
2	0.33	0.14	2.80	0.096
3	0.29	0.019	0.30	0.19
4	0.53	0.24	0.25	0.67
5	0.43	0.050	1.10	0.30
6	0.34	0.040	0.39	0.10
7	0.44	0.025	0.69	0.086
Means±SD[b]	0.41±0.10	0.080±0.082	1.12±1.04	0.23±0.22

a) Expressed in per cent of dose. b) Standard deviation.

From these results, Benhepazone is considered to be almost completely absorbed from the gastrointestinal tract, and then transformed into related compounds. This assumption is supported by the fact that various metabolic products were found in urine.[1]

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Ikuo Matsumoto[*1] : Potassium Carbonate as a Base in the Alkylation of Ethyl Acetamidocyanoacetate.

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Alkylation of ethyl acetamidocyanoacetate followed by hydrolysis is a useful preparative method for α-amino acids and their derivatives. The condensation with alkyl halides has usually been carried out in the presence of sodium ethoxide[1] or sodium hydride.[2] We wish to describe a convenient procedure for the alkylation by using a common and weak base, potassium carbonate as a condensing agent. Its use avoids the need for strictly anhydrous conditions.[1,2]

The reaction is effected in boiling acetone in the presence of anhydrous potassium carbonate and alkylated esters are obtained generally in good yields with reactive primary alkyl halides such as ethyl bromide, allyl chloride, and many benzyl-type halides including

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[1] N.F. Albertson, B.F. Tullar : J. Am. Chem. Soc., **67**, 502 (1945); N.F. Albertson : *Ibid.*, **68**, 450 (1946).

[2] J. Shapira, R. Shapira, K. Dittmer : *Ibid.*, **75**, 3655 (1953).