182°, which was raised up to 185° by further recrystallizations. This compound was to be identical with natural α-sorigenin dimethyl ether (m.p. 185°)[8] and the previously reported γ-lactone I (m.p. 185°)[1] by a mixed melting point determination and comparison of their IR spectra. *Anal.* Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.63; H, 5.34. IR $\nu_{max}^{CHCl_3}$ 1754 (CO) cm^{-1}.

Summary

The synthesis of α-sorigenin dimethyl ether, 3-hydroxymethyl-1,6,8-trimethoxy-2-naphthoic acid γ-lactone (I), by an unequivocal route as shown in chart is described. The reactions employed for preparing the 1-oxo-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthonitrile (VII) from the ethyl 1-oxo-1,2,3,4-tetrahydro-2-naphthoate II via the intermediates, III, IV, and VI, would provide a new method for protecting the keto-group towards lithium aluminum hydride reduction.

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55. Masuo Akagi, Yoneshiro Oketani, Masahiko Takada, and Tetsuya Suga: Studies on Metabolism of 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone. II.[*1] Physiological Disposition and Metabolic Fate of 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone.

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In the previous paper[*1] the estimation of hypnotic, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (MTQ) in biological materials have been reported, and in view of clinical and toxicological importance, a study was made of the physiological disposition and metabolic fate of MTQ.

Experimental and Results

Animals, Diet and Dosage——The rabbits (2.8～3.0 kg., body wt.) were kept on 50 g. of oats and 300 g. of cabbage. MTQ was administered orally in gelatin capsules in a dose of 200 mg./kg. body weight.

Wistar rats (180～200 g., body wt.) were maintained on solid food[*4] and water throughout the the experiments. MTQ (200 mg. or 100 mg./kg. body wt.) was administered by stomach tube as a 2% (w/v) suspension in 5% (w/v) aqueous gum arabic solution. Rabbits and rats were housed in metabolism cages, and urinary collection was made every 24 hr. after administration of the drug.

Estimation of MTQ in Biological Materials——The rats each received MTQ were decapitated and their blood and organs were rapidly removed. The drug in urine, plasma and tissues was measured by a spectrophotometric method described by Akagi *et al.*[*1]

Physiological Disposition of MTQ

Plasma Levels of MTQ after Oral Administration to Human Subjects[*5]——Two human subjects

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*1 Part I. M. Akagi, Y. Oketani, M. Takada: This Bulletin, **11**, 62 (1963).
*2 Nishi-5-chome, Kita-12-jo, Sapporo (赤木満洲雄, 桶谷米四郎, 須賀哲彌).
*3 *Ibid.* (高田昌彦).
*4 Oriental Yeast & Co. Ltd., Tokyo.
*5 The authors are indebted to Prof. N. Suwa of the University of Hokkaido for providing the human blood samples used in this study.

received 0.40 g. of MTQ orally, and the plasma levels of the drug were measured at various time intervals. Peak plasmsa levels, ranging from 19 to 20 mg./100 cc., were noted within 5 hr. after the administration of MTQ, indicating that the absorption of the drug was fairly rapid. Fig. 1 represents plasma levels of the drug in two subjects each of which received a single 0.40 g. oral dose.

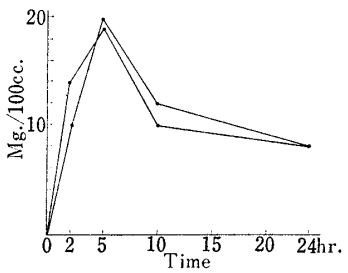

Fig. 1. Plasma Levels of MTQ after Administration of Single 0.40 g. Oral Doses of the Drug to Human Subjects

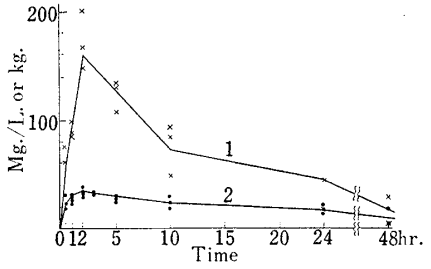

Fig. 2. Plasma Levels (mg./L.) and Concentrations of MTQ in Fat Tissues (mg./kg.) of Female Rats after Oral Administration of 200 mg./kg. of the Drug
1 : fat tissues 2 : plasma

Plasma and Tissue Concentrations of MTQ after Oral Administration to Rats——Female rats each received 200 mg./kg. of MTQ orally and the concentrations of the drug in plasma and in fat tissues were determined (Fig. 2). Both peak plasma level (33 mg./L.) and peak concentration in fat tissues (160 mg./kg.) were obtained within 3 hr. after the administration of MTQ, indicating that the absorption of the drug was fairly rapid. The concentration of the drug in plasma decreased at a slow rate after peak plasma levels were achieved, and at the twenty-fourth hour the drug was still present in plasma presumably due to its sustained absorption from gastrointestinal tract and its relatively slow metabolism. In the experiments using female rats which received an oral dose of 100 mg./kg. of the drug, similar results (peak plasma levels, 30 mg./L.) were obtained.

The distribution of MTQ was examined in the tissues of rats which were killed at various time intervals after oral administration of 200 mg./kg. of the drug (Table I). The concentrations of the drug in liver, kidney and brain were lower than that found in plasma. Its concentration in depot fat, however, was about five times that in plasma at 2 hr.

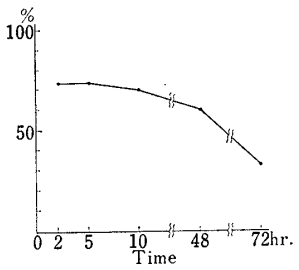

Fig. 3. Distribution of MTQ in Rat Blood

The distribution of MTQ was examined in the blood of rats which were killed at various time intervals after oral administration of 200 mg./kg. of the drug. The amount of the drug in plasma and cells, separated by centrifugation of blood (2 cc.) at 3000 R.P.M. for 30 min., was determined, and the ratio of the amount of the plasma fraction to the total amount in both fractions was calculated.

Fig. 3 shows the distribution of MTQ between plasma and red blood cells of rats which were killed at various time intervals after oral administration. The ratio of the amount of the drug in plasma to that in whole blood was about 74% within 5 hr. after administration.

TABLE I. Distribution of MTQ in Rat Tissues at Various Time Intervals

Time (hr.)	Concentration of MTQ				
	Whole blood (mg./L.)	Fat (mg./kg.)	Liver (mg./kg.)	Kidney (mg./kg.)	Brain (mg./kg.)
2(♀)		203	38	23	19
5(♀)	22	134	16	11	8
10(♂)	14	46	11	17	6
24(♀)	21	94	24	15	11
48(♂)	2	3	0	0	0
72(♂)	1	1	1	0	0

The distribution of MTQ was examined in various tissues of rats which were killed at various time intervals after oral administration of 200 mg./kg. of the drug.

Metabolic Fate of MTQ

Urinary Excretion of MTQ——Human subjects each received 0.20 to 0.50 g. of MTQ orally and urine was collected for the subsequent two days. Less than 2% of the dose was excreted in the urine, indicating that the drug was completely metabolized (Table II). In the experiments using rats receiving 100 mg./kg. of MTQ, the same result obtained (Table III). Tables II and III indicate the slow metabolism of the drug.

Table II. Urinary Excretion of MTQ in Human Subjects given MTQ

Subject No.	Dose (mg.)	Urinary MTQ (%) Time (hr.) (%)		
		12 hr.	24 hr.	48 hr.
1~5	200	0.1~0.3		
6~7	400		0.1~0.2	0.1
8	500		1.4	0
9	500		2.0	

Table III. Urinary Excretion of MTQ in Rats given MTQ

Rat No.	Urinary MTQ (%) Time (hr.) (%)		
	24 hr.	48 hr.	72 hr.
1(♂)	1.7	0.7	0.3
2(♂)	0.9	0.4	0.3
3(♀)	0.5	0.3	

Rats each received 100 mg./kg. of MTQ orally and the supernatant obtained by centrifugation of whole urine (ca. 10 cc.) was diluted to 25 cc. with water. Two cc. of the sample was used for estimation procedure.

Glucuronides Excretion after Oral Administration of MTQ——Urine samples of the aforementioned subjects were examined for total glucuronic acid by the method of Ishidate and Nambara.[1] No increase over the normal excretion of the substance was observed (Fig. 4). A rabbit received 200 mg./kg. of MTQ orally and its urine was collected for the subsequent two days. The urine samples were, then, examined for glucuronic acid by the above method. Results showed that about 20% of the drug might be excreted as conjugates of glucuronic acid (Fig. 4), and they suggested that a metabolite of MTQ was excreted as glucuronide.

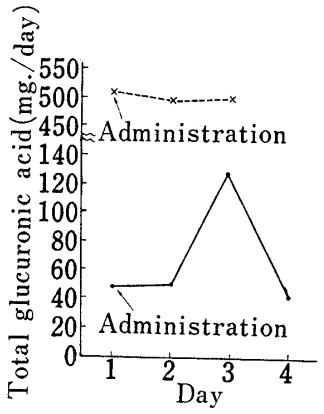

Fig. 4. Urinary Excretion of Total Glucuronic Acid in Human Subject and Rabbit given MTQ

---: human subjects received 0.40 g. of MTQ orally

——: rabbit received 200 mg./kg. of MTQ orally

Etheral Sulfates Excretion after MTQ Administration——The human urine samples were examined for etheral sulfuric acid by the method of Fiske[2] and the results showed that there was no increase over the normal excretion of etheral sulfuric acid. In the experiments using rabbits received 200 mg./kg. of MTQ, the same results were obtained.

1) M. Ishidate, T. Nambara : This Bulletin, **5**, 515 (1957).
2) C. H. Fiske : J. Biol. Chem., **47**, 59 (1921).

Discussion

The action of hypnotics is greatly influenced not only by metabolic transformation in their chemical structures but also by their distribution in various tissues of the body such as in depot fat.[3)]

In rats, a peak plasma level was achieved within 3 hours after oral administration of MTQ and then declined at a slow rate but maintained a fairly high level beyond 24 hours (Fig. 2). In human subjects receiving 400 mg. of the drug orally, a peak plasma level was reached within 5 hours (Fig. 1). The data on the distribution of MTQ in rats (Table I) indicated that the drug localizes in most organ tissues, especially in fat tissues. The concentrations of the drug in liver, kidney and brain were lower than that in plasma. However, its concentration in depot fat in 2 hours after administration was about five times greater than that in plasma (Fig. 2). The drug disappeared almost completely from the body of rat within about 48 hours (Fig. 2, Table I). An early, rapid increase of plasma level along with a high drug concentrations in fat suggest that a rapid absorption of the drug from gastrointestinal tract takes place, and a slow decline of them could be slow metabolic transformation of the drug.

The relation between the concentrations of MTQ in depot fat and in plasma suggests that the persistence of pharmacological drug action is due to the storage of the drug in fat tissues. The action of the drug, therefore, seems to be greatly influenced by the dynamic equilibrium of the drug concentrations between plasma and depot fat.

Urinary excretion of MTQ was less than 2% both in rats and human subjects probably due to the nearly complete biotransformation of the drug.

Glucuronides excretion level after oral administration of 0.40 g. of MTQ in human subjects did not increase significantly over normal excretion rate (Fig. 4). Hence, it may be concluded that in man MTQ is not excreted in an appreciable amount as a glucuronide. However, in a rabbit received 200 mg./kg. of the drug, about 20% increase of glucuronides excretion was noted suggests that one of the benzene rings of MTQ is hydroxylated or that one of the methyl groups of the compound is oxidized to a carboxyl. Further studies on the metabolic fate of MTQ are being conducted.

The authors wish to thank Eisai Co. Ltd., for their supply of 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (Hyminal).

Summary

The physiological disposition and the metabolic fate of hypnotic, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (MTQ), were studied in man, rat and rabbit.

MTQ is rapidly absorbed from the gastrointestinal tract in man and rat. The concentraton of the drug in depot fat is remarkably high compared with that in other tissues in rat. The drug is almost completely metabolized in the body and the rate of biotransformation of the drug is relatively slow.

Glucuronides excretion after oral administration of 200 mg./kg. of MTQ was about 20% in a rabbit.

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3) B. B. Brodie : Fed. Proc., **2**, 632 (1952).