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The Metabolic Fate of 1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (Mepirizole,¹⁾ DA-398) in Rats and Rabbits²⁾

EIGO TAKABATAKE,^{3a)} RYUHEI KODAMA,^{3b)} YOSHIKI TANAKA,
RENZO DOHMORI, HARUO TACHIZAWA
and TAKEO NAITO^{3c)}

Faculty of Pharmaceutical Sciences, Nagasaki University,^{3a)} Kwassui Women's Junior
College^{3b)} and Research Laboratories, Daiichi Seiyaku Co., Ltd.^{3c)}

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The metabolic fate of 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (mepirizole, DA-398) was investigated in rat and rabbit. Four metabolites were isolated as crystals from the urine of medicated rats and identified as 1-(4-methoxy-5-hydroxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (UNM-1), 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-hydroxymethyl-5-methoxypyrazole (UNM-2), 1-(4-methoxy-6-methyl-2-pyrimidinyl)-5-methoxypyrazole-3-carboxylic acid (UAM-1) and 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-hydroxy-5-methoxypyrazole sulfate (URM-1). From the rabbit urine, UAM, UNM-2, UNM-4 (1-(4-methoxy-6-hydroxymethyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole) were isolated and the excretion of UNM-1, UNM-3 (2-hydroxy-4-methoxy-6-methylpyrimidine) and UNM-5 (1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-hydroxy-5-methoxypyrazole) were identified on thin-layer chromatogram. The major metabolite was UAM-1 both in rat and in rabbit.

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (mepirizole, DA-398) is a new analgesic and anti-inflammatory agent synthesized by Naito, *et al.*⁴⁾ Its pharmacological activity is more potent than aminopyrine or oxyphenbutazone.⁵⁾ The authors have studied the metabolic fate of mepirizole in rats using the compound labeled with ¹⁴C in the 3-position of the pyrazole moiety and in rabbits using the unlabeled compound. This paper is concerned with the isolation of the urinary metabolites of mepirizole and the elucidation of their chemical structures.

Experimental

Materials—Mepirizole was prepared according to the method of Naito, *et al.*⁴⁾ Mepirizole-¹⁴C labeled in the 3-position of pyrazole moiety (specific activity, 1.07 μ Ci/mg) was purchased from Daiichi Pure Chemical Co., Ltd. (Tokyo). PPO (2,5-diphenyloxazole) and dimethyl POPOP (1,4-bis(4-methyl-5-phenyl-2-oxazolyl)-benzene) were purchased from Packard Instrument Co., Inc.

Administration of Mepirizole—Male Wistar rats (230—270 g) and male rabbits (3—4 kg) were used. They fed CA-1 Rat Diet (Nihon CLEA Co.) or RC-5 Rabbit Diet (Oriental Co.) and tap water *ad libitum*. Mepirizole was dissolved in water and administered orally in a dose of 120 mg/kg to rats or 180 mg/kg to rabbits. The urine free from feces was collected in the individual metabolic cages.

Thin-Layer Chromatography—Thin-layer chromatography was carried out on silica gel plates (Kieselgel HF₂₅₄ and GF₂₅₄ Merck, activated at 120° for 60 min, 0.25 mm). The solvent systems used were A) benzene—

1) Japanese accepted name.

2) Presented in part at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April, 1969 and at the Meeting of Kyushu Branch, the Pharmaceutical Society of Japan, Fukuoka, September, 1969.

3) Location: a) Bunkyo-machi, Nagasaki; b) Higashiyamate-machi, Nagasaki; c) Minamifunabori-cho, Edogawa-ku, Tokyo.

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MeOH-AcOEt (6:3:1), B) CHCl₃-acetone-MeOH (8:1:1), C) benzene-AcOEt-MeOH (5:4:1), D) MeOH-benzene-CHCl₃ (8:1:1), E) benzene-EtOH (9:1) and F) benzene-EtOH-Et₃N (18:2:1). The resulting chromatograms were visualized under UV light (2536 Å) or after spraying with Dragendorff reagent. Radioactivity was determined by using a thin-layer radio-chromatogram scanner (Japan Radiation and Medical Electronics, Inc., Tokyo).

Radioisotopic Analysis—A tenth to fifth milliliter of radioactive samples (urine, extract or eluate) was dissolved directly into 15 ml of *p*-dioxane phosphor consisting of 100 g naphthalene, 7 g PPO, 0.3 g dimethyl POPOP and 900 ml *p*-dioxane. Radioactivities were measured by Beckman liquid scintillation spectrometer (Model DPM-100); corrections for counting efficiency were made using ¹³⁷Cs as the external standard.

Extraction of Metabolites—The urine sample, after concentrating to a third of the volume (in the case of rat) or directly (in the case of rabbit), was extracted continuously with AcOEt for 75 hr (UN-fraction). The urinary layer was adjusted to pH 1.0 with HCl and extracted again with AcOEt (UA-fraction). The residue was neutralized with NaOH to give UR-fraction.

Quantitative Determination of the Metabolites from Rabbit Urine—The UA- and UN-fraction from 48 hr urine of each rabbit received 600 mg of mepirizole were evaporated to dryness and dissolved in MeOH, 25 ml for UN and 100 ml for UA respectively. Five milliliters of the MeOH solutions were applied to 2×20 cm Sephadex LH-20 column, which were eluted with 1% NaCl solution. The first 100 ml eluates were collected, evaporated to dryness and dissolved in 25 ml of MeOH. Aliquots of the MeOH solution were spotted on silica gel plate (Kieselgel G Merck, 0.75 mm) and developed with the solvent system A for the determination of unchanged mepirizole, UNM-2, -3, -4 and UAM-1 or the solvent system C for UNM-1 and UNM-5.⁶⁾ Each spot corresponding to these materials was scraped off under UV light and extracted with MeOH.

Control urine was also subjected to the same procedure. The areas of the plate corresponding to the unchanged mepirizole and the metabolites were scraped off, eluted and used as the blank.

The amount of each substance was determined from the absorbance of UV (mepirizole, UAM-1, UNM-2, and UNM-4 at 251 mμ, UNM-1 at 256 mμ, UNM-3 at 275 mμ and UNM-5 at 273 mμ). Recovery rates of each substance were 98.5% on the average. Excretion rates were calculated correcting the molecular weight of the metabolite.

Result

Recovery of Radioactivity in Rat Urine

After medication of mepirizole-¹⁴C in 3 rats, the recovery of radioactivity in urine during 48 hr averages about 62%, of which 12% was detected in the UN-fraction, 28% in the UA-fraction and 22% in the UR-fraction, respectively (Table I).

Fig. 1 shows the radioactive scan of the thin-layer chromatogram of each fraction. Of the UN-fraction, two higher peaks were detected at *Rf* 0.25 (UNM-1) and at *Rf* 0.51 (UNM-2) by the solvent system F. The thin-layer chromatogram of UA-fraction developed with the solvent system D showed a broad peak (UAM-1) at *Rf* 0.25 and that of UR-fraction using the same solvent system showed one peak (URM-1) at *Rf* 0.48.

TABLE I. Recovery of ¹⁴C in the Urine of Rats after Oral Administration of Mepirizole-¹⁴C

Rat No.	0—24 hr (%)	24—48 hr (%)	Total (%)
1	35.9	20.4	56.3
2	60.1	7.4	67.5
3	51.5	10.9	62.4
		mean	62.1

Isolation of the Metabolites from Rat Urine

The combined 48 hr urine from 3 rats received mepirizole-¹⁴C and 31 rats received unlabeled compound (total 1.1 g) was used for the isolation of metabolites. The UA-fraction was con-

6) The authors adopted names of UAM-1, UNM-1, -2, -3, -4, -5 and URM-1 for the metabolites obtained from UA-, UN- and UR- fraction.

centrated to syrup and the residue was dissolved in water. The aqueous solution was adjusted to pH 6 with dil. NaOH and poured onto the top of the column packed with strongly basic ion-exchange resin (Dowex 1-X4; OH⁻ type) and then the column was washed thoroughly with water. By the treatment with 1N HCl, colorless crystals appeared in the column. The resin was taken out of the column and the crystals were extracted with MeOH and then recrystallized from aqueous MeOH to obtain as colorless needles (63 mg), mp 193–195° (UAM-1).

The UN-fraction was concentrated to syrup and the residue was purified using silica gel (30 g) chromatography. The column was eluted with CHCl₃ 100 ml, AcOEt-CHCl₃ (1:1) 100 ml, AcOEt 300 ml, MeOH-AcOEt (1:9) 200 ml and MeOH 100 ml in succession. A material eluted with CHCl₃ (*R_f*: 0.55, solvent system F) was proved to be unchanged mepirizole by thin-layer chromatography and the reverse isotope dilution method. A metabolite eluted with AcOEt-CHCl₃ (1:1) was recrystallized from AcOEt to obtain as colorless prisms (17 mg), mp 203–205° (UNM-1). The crude product eluted with AcOEt and MeOH-AcOEt (1:9) was rechromatographed on silica gel (20 g) and the column was eluted with CHCl₃ 230 ml and MeOH-CHCl₃ (1:99) 200 ml. A metabolite obtained from the MeOH-CHCl₃ (1:99) eluate was washed with ether to obtain colorless powder (7 mg), mp 128–131° (UNM-2).

To the UR-fraction (aqueous solution), 5 g activated charcoal was added and the mixture was stirred at room temperature for 24 hr. After adsorption process, the charcoal was separated by centrifugation from the aqueous solution and the adsorbed metabolite was eluted with conc. NH₄OH-MeOH (1:13). The residue obtained from the eluate was dissolved in MeOH-AcOEt (1:9) and poured onto silica gel (20 g) column. The column was eluted with MeOH-AcOEt (1:4) 160 ml and MeOH 40 ml. The fractions eluted with MeOH-AcOEt (1:4) were treated with a small volume of EtOH to give colorless powder (7 mg), mp 204–207° (decomp.) (NH₄ salt of URM-1).

Fig. 1. The Radioactive Scan of Thin-Layer Chromatogram of Each Extract

solvent system A		solvent system B	
1.0			
		mepirizole	○
mepirizole	○	UNM-5	○
UNM-5	○	UNM-1	○
UNM-1	○	UNM-2	○
UNM-2	○	UNM-4	○
UNM-3	○	UNM-3	○
UNM-4	○		
UAM-1	○	UAM-1	○
0			
UA	UN	UA	UN

Fig. 2. Thin-Layer Chromatograms of UN and UA Fraction from Rabbit Urine

The samples for elemental analyses were prepared separately using unlabeled compound in the same way as described above. They were identical with the radioactive samples in all respects.

Detection of the Urinary Metabolites from Rabbit Urine on Thin-Layer Chromatogram

On the thin-layer chromatograms of rabbit urine extracts shown in Fig. 2, at least 9 spots were detected in UN-fraction and 2 spots in UA-fraction. The *R_f* values of these metabolites developed with the six solvent systems were listed in Table II. Among these, a spot of *R_f* 0.63 by the solvent system A was identified as unchanged mepirizole after comparing with authentic sample. Three metabolites, UAM-1, UNM-2, and UNM-4, were isolated and

TABLE II. *R_f* Values of Mepirizole and Its Metabolites on Thin-Layer Chromatogram

Compound	Solvent systems					
	A	B	C	D	E	F
Mepirizole	0.63	0.73	0.39	0.65	0.39	0.55
UAM-1	0.08	0.03	0.02	0.25	0.00	0.04
UNM-1	0.56	0.61	0.27	0.63	0.30	0.25
UNM-2	0.50	0.55	0.17	0.60	0.27	0.51
UNM-3	0.45	0.42	0.13	0.58	0.19	0.39
UNM-4	0.42	0.49	0.15	0.46	0.19	0.48
UNM-5	0.59	0.63	0.35	0.69	0.31	0.43
URM-1 (NH ₄ salt)	0.20	0.03	0.00	0.48	0.01	0.05

characterized. Other three metabolites, UNM-1, UNM-3, and UNM-5, were identified by comparing them with the synthetic samples.⁷⁾

Isolation of the Metabolites from Rabbit Urine

Ten grams of mepirizole in total amount was given to rabbits for the isolation study and the urines were collected during 24 hr.

The UA-fraction was dissolved in water, adjusted to pH 1.0 with conc. HCl, and extracted repeatedly with ether. After evaporation of the ether, the crystals produced were collected and recrystallized from AcOEt-EtOH (1:1) to give 3.2 g of colorless needles, mp 193—195°. This compound was identical with UAM-1 from rats.

The UN-fraction dissolved in a small volume of acetone was applied to a 3×40 cm Florisil (100—200 mesh) column. The column was eluted with benzene 500 ml, benzene-AcOEt (1:1) 1000 ml, benzene-AcOEt (3:7) 1500 ml, AcOEt 1000 ml, AcOEt-acetone (1:1) 3000 ml, acetone 1000 ml, acetone-MeOH (1:1) 500 ml and MeOH 500 ml in succession.

After evaporation of AcOEt-acetone (1:1) eluate from Florisil column, the crystals produced were collected and recrystallized from benzene to give 270 mg of colorless needles, mp 134—135°. This metabolite was identical with UNM-2 from rat urine.

Acetone eluate from Florisil column was evaporated to dryness and dissolved in a small volume of AcOEt and applied to 2×30 cm alumina column. The column was eluted with benzene 500 ml, benzene-AcOEt (1:1) 500 ml, AcOEt 300 ml, acetone 300 ml, and MeOH 200 ml in succession. Evaporation of the benzene-AcOEt (1:1) eluate and the recrystallization from benzene-petr. ether (1:1) gave 57 mg of colorless needles, mp 152.5—153° (UNM-4).

Structure Elucidation of the Metabolites⁸⁾

The structures of these metabolites were elucidated by the elemental analyses and the spectral data of infrared (IR), ultraviolet (UV) (Table IV) and nuclear magnetic resonance (NMR) (Table III).

UAM-1—The IR spectrum (KBr) had a characteristic band of carbonyl group at 1740 cm⁻¹. The NMR spectrum in CD₃OD indicated the disappearance of the methyl group located on 3-position of pyrazole moiety. It gave positive ferric hydroxamate test. *Anal.* Calcd. for C₁₁H₁₂O₄N₄: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.45; H, 4.44; N, 20.97 (from rat), C, 49.42; H, 4.62; N, 20.68 (from rabbit). The structure of UAM-1 was elucidated 1-(4-methoxy-6-methyl-2-pyrimidinyl)-5-methoxypyrazole-3-carboxylic acid.

UNM-1—The molecular weight was measured to be 254±5 by the vapor pressure method. The NMR spectrum in CD₃OD indicated the disappearance of a proton signal of

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8) The syntheses of these metabolites will be reported in the following paper.⁷⁾

pyrimidine-5-position. The UV spectrum showed a typical pattern of 1-pyrimidinylpyrazole derivatives (Table IV). *Anal.* Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.95; H, 5.77; N, 22.11 (from rat). From these data, UNM-1 was estimated as 1-(4-methoxy-5-hydroxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole.

UNM-2—The UV spectrum in MeOH showed maximum at 251 m μ . This was similar to that of mepirizole and suggested the remaining of 1-pyrimidinylpyrazole system. The IR spectrum (KBr) had a characteristic band at 3300 cm^{-1} , which suggested the presence of a hydroxyl group. The NMR spectrum in DMSO- d_6 indicated the presence of a primary alcohol at 4.39 ppm (2H, doublet, $J=4$ Hz, $-CH_2-$), 5.15 ppm (1H, triplet, $J=4$ Hz, $-OH$) instead of the disappearance of the methyl group on pyrazole-3-position of mepirizole. *Anal.* Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.38; H, 5.81; N, 22.08 (from rat), C, 52.80; H, 5.60; N, 21.84 (from rabbit). The structure of UNM-2 was presumed to be 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-hydroxymethyl-5-methoxypyrazole from above data.

UNM-4—The IR spectrum had a characteristic band at 3330 cm^{-1} and suggested the presence of a hydroxyl group. The NMR spectrum (in $CDCl_3$) indicated that the methyl group on pyrimidine-6-position of mepirizole disappeared and was replaced with methylene group (4.71 ppm) and hydroxyl group (4.33 ppm) which disappeared by the treatment with D_2O . *Anal.* Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.54; H, 5.84; N, 22.14 (from rabbit). The structure of UNM-4 was estimated as 1-(4-methoxy-6-hydroxymethyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole.

URM-1—This metabolite was obtained as ammonium salt and it contained sulfur atom. The IR spectrum (KBr) showed characteristic bands of NH_4 group at 3100–3200 cm^{-1} and SO_2 group at 1280 cm^{-1} . A proton signal of pyrazole-4-position of mepirizole disappeared in the NMR spectrum of URM-1. *Anal.* Calcd. for $C_{11}H_{13}O_6N_4S \cdot NH_4$: C, 38.03; H, 4.94. Found: C, 37.79; H, 5.17 (from rat). Thus, the structure of URM-1 was estimated as 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-hydroxy-5-methoxypyrazole sulfate.

TABLE III. NMR Spectral Data of Mepirizole and Its Metabolites^{a)}

Compounds	Solvents	CH ₃ (pyrazole-C ₃ and pyrimi- dine-C ₆)	OCH ₃ (pyrazole-C ₅ and pyrimi- dine-C ₄)	H (pyra- zole-C ₄)	H (pyrimi- dine-C ₅)	Other groups ^{b)}	
Mepirizole	$CDCl_3$	2.30, 2.51	3.93, 4.01	5.51	6.42		
	CD_3OD	2.23, 2.41	3.91, 3.97	5.63	6.51		
	DMSO- d_6	2.17, 2.40	3.88, 3.93	5.69	6.67		
UNM-1	CD_3OD	2.23, 2.38	3.92, 4.05	5.63			
UNM-2	DMSO- d_6	2.39	3.92, 3.94	5.83	6.71	4.39 (CH ₂ , d, $J=4$ Hz)	5.15 (OH, t, $J=4$ Hz)
UNM-4	$CDCl_3$	2.26	3.92, 3.99	5.47	6.60	4.71 (CH ₂)	4.33 (OH)
UAM	CD_3OD	2.43	3.93, 3.93	6.17	6.58		
URM ^{c)}	CD_3OD	2.31, 2.44	4.02, 4.23		6.60		

a) Measured at 100 MHz on JNM-4H-100 (Japan Electron Optics Lab. Tokyo Japan). Chemical shifts are given in ppm from TMS as an internal standard. Each signal is singlet except especially mentioned.

b) abbreviation; d, doublet; t, triplet

c) NH_4 -salt

Identification of the Metabolites

UNM-3—After treating mepirizole with 15% H_2O_2 in a boiling water bath, the separation by silica gel chromatography gave colorless needles, mp 209–210° which were identical

with 2-hydroxy-4-methoxy-6-methylpyrimidine⁹⁾ in UV, IR or NMR spectra. The UNM-3 was indistinguishable from this compound on thin-layer chromatograms developed with every solvent system used.

UNM-1—It was not isolated from rabbit urine but its excretion was established on thin-layer chromatogram with comparing with the synthetic sample.⁷⁾

UNM-5—It was identified as 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-hydroxy-5-methoxypyrazole after comparing its chromatographic pattern with the synthetic sample.⁷⁾

Excretion Rates of Mepirizole and Its Metabolites in Rabbit Urine

The results are shown in Table IV. The fate of about 50% of mepirizole administered to rabbits were clarified. The excretion of unchanged drug was very small, less than 1%. The major metabolite was UAM-1 which was about 37%. UNM-2, probably the precursor of UAM-1, was also excreted at about 5%. UNM-4, another oxidation product of the methyl group was excreted at 2–3% but the corresponding carboxylic acid metabolite has not been detected. Both UNM-1 and UNM-5, hydroxy metabolites on either ring, were excreted at the same rate, about 1%. UNM-3 was determined at about 2%. The fate of the residual 50% is not clear at present.

TABLE IV. Physicochemical Properties and Excretion Rates of Mepirizole and Its Metabolites

Fraction	Metabolites	mp (°C)	UV $\lambda_{\text{max}}^{\text{MeOH}}$ m μ (log ϵ)	Excretion rates (%)	
				Rat ^{a)}	Rabbit ^{b)}
UN	Mepirizole	89–90	251 (4.23)	0.5–1.0	0.85 ± 0.67
	UNM-1	203–205	256 (4.24)	4–6	0.92 ± 0.37
	UNM-2	134–135	251 (4.21)	3–5	4.99 ± 0.61
	UNM-3 ^{c)}	209–210	275 (3.34)	—	2.35 ± 1.20
	UNM-4	152.5–153	251 (4.27)	—	2.67 ± 0.65
	UNM-5 ^{d)}	195–198	273 (4.18)	—	1.04 ± 0.55
UA	UAM-1	193–195	251 (4.21)	25	37.41 ± 4.56
UR	URM-1	204–207 (decomp.)	263 (4.29)	18–19	

a) Calculated from radioactivity in urine of 3 rats.

b) Determined by means of thin-layer chromatography mentioned in text.
Mean ± standard deviation of 5 rabbits.

c) The sample obtained from mepirizol by H₂O₂-treatment.

d) synthetic sample⁷⁾

Discussion

Mepirizole may be biotransformed by several pathways such as 1) oxidation of the methyl group to hydroxyl and further to carboxylic acid, 2) hydroxylation on pyrazole or pyrimidine ring, 3) demethylation of methoxy groups, 4) cleavage between the two rings, 5) conjugation, etc.

The major urinary metabolite in both rat and rabbit was UAM-1, carboxylic acid derivative at the 3-position of pyrazole moiety. 3,5-Dimethylpyrazole¹⁰⁾ or 3,5-dimethylisoxazole¹¹⁾ is oxidized to 5-methylpyrazole-3-carboxylic acid or 3-methylisoxazole-5-carboxylic acid giving an active metabolite in either case. Thus, the oxidation of the methyl group to carboxylic acid is common in these substances. However, the carboxylic metabolite of mepirizole, UAM-1, had no analgesic or blood glucose decreasing activity.

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3-Hydroxymethyl metabolite of the pyrazole ring, UNM-2, is probably the precursor of UAM-1. This metabolite was isolated in both rabbit and rat. 6-Hydroxymethyl metabolite of the pyrimidine ring, UNM-4, was also isolated from rabbit urine but the corresponding carboxylic acid metabolite has not been detected, yet. On the other hand, UNM-4 has not been detected in rat urine, either. It is not apparent at present why the methyl group on pyrazole ring is more sensitive to biotransformation than the methyl group on the pyrimidine ring.

Chart 1

- a)* Isolated from rat urine and identified from rabbit urine.
b) Identified from rabbit urine.
c) Isolated from rat urine.
d) Isolated from both rat and rabbit urine.
e) Isolated from rabbit urine.

The hydroxylation product on pyrimidine ring, UNM-1, was isolated from rat urine and identified in rabbit urine as free form. Another hydroxylation product on pyrazole ring, UNM-5, was identified as free form in rabbit urine but isolated as sulfate from rat urine. This type of hydroxylation is also a common pathway with 3,5-dimethylpyrazole¹²⁾ or antipyrine.^{13,14)} Tanaka¹⁵⁾ presented chromatographic evidence of a sulfate ester of 4-hydroxyantipyrine in the urine of the rabbits dosed with antipyrine. The formation of URM-1 is probably the similar pathway as in this case. It was reported that the rabbits dosed with sulfamethazine excreted the oxidation product hydroxylated on the 5-position of pyrimidine ring.¹⁶⁾ It is interesting that mepirizole was hydroxylated on the *p*-position of the aromatic ring bound to pyrazol ring, as the biotransformation of phenylbutazone having similar pharmacological properties.¹⁷⁾

One of the cleavaging products between two rings was identified but the fate of another pyrazole moiety is not clear.

About 50% of the radioactive compound administered in rats was accounted by the four metabolites which were isolated in crystalline form. The quantitative determination clarified the fate of about half of mepirizole given to rabbits.

By summarizing our investigation described above, the authors propose the metabolic pathway of mepirizole in rat and rabbit as shown in Chart 1.

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