Physiologic Disposition and Metabolic Fate of Indomethacin Analogs I: 1-*p*-Chlorobenzylidenyl-5-methoxy-2-methylindene-3-acetic Acid

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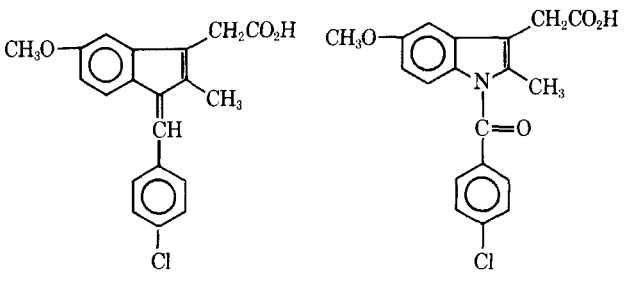
Abstract □ The title compound was well absorbed after oral administration to the dog and rat. About 70–90% of a single dose was excreted in the urine and feces in 4 days, with fecal elimination being predominant. Peak plasma levels were observed in both species at 1–2 hr. after oral administration. The plasma half-life was 1–2 and 4 hr. in the dog and rat, respectively. The compound was widely distributed but not concentrated in rat tissues and was highly bound to plasma proteins. About 35–44% of the dose was excreted in dog and rat bile, with excretion in the dog appearing to be inversely proportional to dose. The acyl glucuronide of the title compound was identified as a major metabolite in dog bile. Significant localization of the title compound and/or its metabolites in inflamed rat tissue was also demonstrated.

Keyphrases □ Indomethacin, indene analogs—physiologic disposition and metabolites, dogs, rats □ 1-*p*-Chlorobenzylidenyl-5-methoxy-2-methylindene-3-acetic acid—physiologic disposition and metabolites, dogs, rats □ GLC—determination

Several pharmacologically active compounds similar to indomethacin[1] have been discovered to date. An indene analog, 1-*p*-chlorobenzylidenyl-5-methoxy-2-methylindene-3-acetic acid (I), synthesized by Shen *et al.* (1–3), has anti-inflammatory activity nearly the same as indomethacin but reduced gastrointestinal effects[2]. Pharmacologic activity of I is at least partly stereospecific, since the *trans*-isomer, in which the *p*-chlorophenyl ring is opposite the phenyl ring of the indole nucleus, is only one-fifth as active as the *cis*-form. I is isosteric with indomethacin. Unlike the *N*-acyl indoles, it is stable under acidic and alkaline conditions. The present report describes studies on the absorption, excretion, tissue distribution, and metabolic fate of the *cis*-isomer of I.



I indomethacin

METHODS AND MATERIALS

I labeled with ^{14}C in the benzylidene bridge carbon atom, with a specific activity of 1.7 μc./mg., was used. The melting point (168–169°) and UV absorption spectrum in methanol (λ_{max}. 238, 288, and 340 nm.) were identical with the values observed for the authentic drug. Radioactive I showed a single component after paper chromatography.

Absorption and Excretion Studies—Mature male Sprague-Dawley rats and beagle dogs of both sexes were fasted overnight prior to dosing. I was administered to rats in solutions prepared by dissolving the compound in a small volume of dimethylacetamide. A solubilizing agent[3] was added to this solution before diluting with saline. The ratio of the three solvents was approximately 1:3:100 (v/v) at drug concentrations of about 3 mg./ml. I was administered to dogs in methylcellulose[4] suspensions for excretion studies and in capsules for plasma level determination. After drug administration, animals were placed in individual stainless steel cages designed for separate collection of urine and feces. Urine was frozen as collected in dry ice-cooled containers. Rats were allowed standard laboratory chow and water *ad libitum*. Dogs were fed commercial dogfood once daily with water available *ad libitum*.

Biliary Excretion Studies—Bile was collected from unanesthetized dogs 1 week after surgical preparation of bile fistulas, as previously described (4). The common bile duct of a rat was also cannulated with polyethylene tubing under methohexital anesthesia. The incision was closed, and the animal was allowed to recover before dosing.

Inflamed Tissue Studies—Left hind feet of six male rats were injected with 0.1 ml. of a 10% suspension of brewer's yeast. After 2 hr., the animals were given I-^{14}C orally (10 mg./kg). One hour later, the rats were sacrificed and both hind feet were cut off, weighed, and dissolved in 9 volumes of 1 *N* KOH with heat. After cooling, the solutions were assayed for radioactivity content.

Determination of Radioactivity—Radioactivity was measured in a Packard Tri-Carb liquid scintillation counter. Aliquots of plasma and urine (0.1–0.5 ml.) were added directly to the scintillation fluid for assay of ^{14}C. The scintillation solution consisted of 80 g. of naphthalene, 7 g. of 2,5-diphenyloxazole, 0.3 g. of 1,4-bis-2-(5-phenyloxazolyl)-benzene, and 30 g. of a thixotropic gel[5] in 1 l. of dioxane. Bile was diluted 200 times with water before counting. Feces and tissues were homogenized in a suitable volume of water, and an aliquot was decolorized prior to counting (5). Red cells were diluted 15 times with water, and an aliquot was decolorized prior to counting. The counting efficiency was determined by internal standardization. In the case of particulate samples, the counting efficiency was also estimated by the channels ratio method (6).

Determination of I—I was measured in biological samples by either of the following procedures.

Procedure A—One milliliter of plasma or urine was added to 2 ml. of 1 *N* hydrochloric acid and 25 ml. of heptane (containing 3% isomayl alcohol) in a 45-ml. glass-stoppered centrifuge tube. The tube was shaken for 10 min. and centrifuged, and 20 ml. of the organic phase was transferred to a similar tube containing 5 ml. of 0.1 *N* sodium hydroxide. After shaking for 5 min., the tube was centrifuged and the organic phase was removed by aspiration. Two milliliters of the aqueous phase was counted if radioactive samples were assayed. Otherwise, the absorbance of the alkaline solution was measured at 337 nm. and used to calculate I in the sample. I added to plasma and urine in amounts of 1–25 mcg. was recovered with adequate precision (mean ± *SE* = 82 ± 2% for plasma; mean ± *SE* = 90 ± 2% for urine). Recoveries of 5–100 mcg. amounts of I added to tissue homogenates were somewhat lower but of adequate precision (mean ± *SE* = 68 ± 3%).

Procedure B—Nonradioactive drug was also measured by GLC. The 5-fluoro analog of I was used as a mass internal standard as described by Sparagana (7). The instrument, Hewlett-Packard model 810 with dual-flame detectors, was equipped with coiled glass columns [1.8 m. × 0.64 cm. (6 ft. × 0.25 in.)] packed with 3%

[1] Registered under the tradename of Indocin, Merck & Co., Inc.
[2] Unpublished data of Dr. C. A. Winter and Dr. D. A. Brodie.
[3] Emulphor-EL620, General Aniline and Film Corp.
[4] Methocel.
[5] Cab-O-Sil.

Table I—Excretion of Radioactivity by Rats and Dogs after Administration of Labeled I[a]

Sample	Day	Rat		Dog
		Oral Dose	Intravenous Dose	Oral Dose
Urine	1	4.2 (2.6–5.7)	6.4 (5.3–8.0)	4.9 (3.0–6.8)
	2	3.2 (1.8–5.3)	3.0 (2.2–3.6)	1.4 (0.3–3.7)
	3	1.2 (0.7–1.5)	1.5 (1.0–2.0)	0.3 (0.1–0.6)
	4	0.8 (0.4–1.2)	0.4 (0.3–0.5)	—
	Total	9.4 (6.9–13.1)	11.3 (8.8–12.8)	6.6 (3.4–10.7)
Feces	1	1.4 (0.5–2.8)	3.6 (1.3–5.2)	44.8 (0.4–81.6)
	2	36.3 (33.9–39.2)	35.1 (27.3–41.8)	25.8 (2.4–73.0)
	3	15.7 (7.9–21.3)	17.1 (11.1–21.8)	12.0 (1.9–42.0)
	4	8.2 (4.3–16.7)	5.9 (3.2–8.0)	—
	Total	61.6 (59.0–63.8)	61.7 (57.5–66.9)	82.6 (75.4–91.5)
Total		71.0 (69.1–72.1)	73.0 (66.6–78.6)	89.2 (78.8–96.7)

[a] Four rats per group were given 3 mg./kg., and four dogs received 0.1 mg./kg. Results are expressed as percent of administered dose, with range shown in parentheses.

QF-1 on Chromasorb G, 100–120 mesh[6]. Operating conditions were as follows: oven, 260°; injection port, 295°; detector, 305°; and helium flow, 50 ml./min.

The procedure used was as follows. One milliliter of plasma was added to a 15-ml. glass-stoppered centrifuge tube with a finely tapered tip[7] containing 5 mcg. of 5-fluoro-I (in 0.05 ml. of ethanol) and 0.1 ml. of 6 *N* HCl. The tube was mixed for 1 min. (Vortex mixer) and centrifuged. The heptane phase was transferred to a similar tube, mixed for 1 min. with 1 ml. of 1 *N* sodium hydroxide, and centrifuged. The aqueous phase was transferred to a third tube, mixed for 1 min. with 0.1 ml. of 6 *N* HCl and 0.1 ml. chloroform, and centrifuged. After careful removal of the aqueous phase by aspiration, the chloroform extract was evaporated to dryness in a stream of nitrogen with the tube immersed in warm water. The residue was dissolved in 30 μl. of ether and treated with 3 μl. of an ethereal solution of diazomethane (generated from *N*-nitrosomethylurea). After 5 min., the ether and excess reagent were removed by placing the tube in warm water. The residue was dissolved in 10 μl. of ether, and 2 μl. was injected into the chromatograph. The retention times of the methyl esters of I and the 5-fluoro internal standard were 5.7 and 3.5 min., respectively.

A standard curve was constructed by plotting the peak height ratios *versus* concentration ratios of I to the internal standard. The peak height ratio obtained from unknowns was then used to estimate the amount of I present.

TLC—TLC was performed on commercially prepared fluorescent silica gel GF-coated glass plates. The coating thickness was 250 μ. Reference compounds were located as dark spots under UV light. Radioactive compounds were detected with a Packard model 7201 radiochromatogram scanner.

RESULTS

Absorption and Excretion—The excretion of radioactive material in the urine and feces by rats after oral and intravenous administration of I (3 mg./kg.) is shown in Table I. A major fraction (61%) of the dose was excreted in the feces, with only minor amounts (10%) appearing in the urine. The similarity in excretory patterns of oral and intravenous doses demonstrated that I was completely absorbed in the rat. Rats given a higher dose of I orally (25 mg./kg.) excreted 15 and 29% of the dose in the urine and feces, respectively, in 72 hr.

An even higher fraction (82%) of an oral dose was excreted in dog feces (Table I), but this finding did not indicate poor oral absorption since the drug was at least partly excreted in dog bile. The excretory pattern in the dog was similar to that obtained in rats. The drug was also well absorbed in guinea pigs, since 24% of orally administered I was excreted in the urine in 72 hr. compared to 37% after intraperitoneal administration.

Plasma Levels of I—The concentrations of I in plasma of rats given labeled I orally and intravenously (3 mg./kg.) are shown in Table II. When the plasma was extracted as described in *Procedure A*, all of the radioactivity was recovered. TLC of these extracts gave only a single radioactive peak, which was identical with that of authentic I, as shown in Table III. These results indicated that only unchanged I was present in rat plasma. Levels reached a maximum at 1–4 hr. after oral administration. The half-life of drug in the plasma after an intravenous dose was approximately 4.5 hr.

Plasma levels of I in dogs given a single dose of the drug orally (20 mg./kg.) are shown in Table II. Concentrations were maximal after 1–2 hr. and were nearly equal to those found in rats given a much lower dose. The levels declined thereafter, with an apparent half-life of 1–2 hr. Plasma levels of I in dogs given a single oral dose (20 mg./kg.) of the drug as the sodium salt were significantly lower at 2 hr. than levels in those animals given I as the free acid.

Plasma concentrations of I after administration of multiple doses to rats and dogs are shown in Table IV. As indicated, plasma levels in rats given multiple doses of I were significantly lower than concentrations obtained after single doses. Levels in dogs given multiple doses of I were not significantly different from those observed after a single dose, except at 2 hr. when the multiple-dose level was significantly lower ($p < 0.05$).

Table II—Plasma Concentrations of I in Rats and Dogs after a Single Dose of Labeled I[a]

Hours	Rat		Dog	
	Intravenous Dose	Oral Dose	Oral Dose (FA)	Oral Dose (Na)
0.25	23.4 ± 1.3	—	—	—
0.5	21.1 ± 1.4	6.3 ± 0.2	—	—
1	17.6 ± 1.4	12.4 ± 2.0	10.6 ± 3.1	10.2 ± 0.9
2	15.7 ± 1.0	11.6 ± 1.0	11.7 ± 2.0	4.8 ± 0.3
4	13.1 ± 1.3	11.9 ± 0.1	1.4 ± 0.4	1.0 ± 0.1
6	11.4 ± 1.0	9.4 ± 2.0	1.7 ± 0.7	1.9 ± 0.2
16	—	7.3 ± 0.3	—	—
24	6.1 ± 1.0	10.2 ± 2.4	0.4 ± 0.1	0
48	2.4 ± 0.3	2.4 ± 1.0	—	—

[a] Approximately 20 rats in each group received 3 mg./kg. Eight dogs received 20 mg./kg. as the free acid (FA) or sodium salt (Na). Results are expressed as micrograms of I per milliliter (mean ± *SE*). Plasma of rats was assayed by *Procedure A* (*Methods*) and that of dogs by *Procedure B* (*Methods*).

Table III—TLC of Apparent I Extracted from Rat Tissues and Authentic Drug[a]

Compound	R_f				
	Solvent A	Solvent B	Solvent C	Solvent D	Solvent E
I	0.51	0.74	0.59	0.33	0.54
Apparent I	0.51	0.74	0.59	0.33	0.54

[a] Apparent I was extracted (*Procedure A*) from the liver, small intestine, stomach, and plasma of rats 2 hr. after administration of I-^{14}C. The solvent systems used were as follows: A, 2-propanol–15 *N* ammonia (8:2); B, 2-propanol–acetic acid (91:5); C, chloroform–acetic acid (95:5); D, 1-butanol saturated with water; and E, ethyl acetate–2-propanol–5 *N* ammonia (5:4:3).

[6] Applied Science Labs, Inc.
[7] Pesce Glass Co., Kennett Square, Pa.

Table IV—Plasma Levels of I in Rats and Dogs after Multiple Daily Doses[a]

Hours	Rat		Dog	
	Single Dose	Multiple Dose	Multiple Dose (20)	Multiple Dose (40)
0.5	—	—	2.8 ± 2.0	7.1 ± 3.8
1	—	—	6.2 ± 3.1	8.0 ± 3.6
2	128.2 ± 7.0	66.1 ± 18.1	3.9 ± 0.8	5.1 ± 1.3
4	97.3 ± 2.9	66.2 ± 5.4	3.0 ± 2.1	2.1 ± 1.4
6	99.9 ± 1.2	63.7 ± 1.4	0	0
24	—	—	0	0

[a] Twelve rats received 30 mg./kg. of I orally daily for 10 days, after which they received, along with 12 additional rats, a single oral dose (30 mg./kg.) of I-^{14}C. Differences between groups were significant ($p < 0.05$) at all times. Four dogs in each group received daily oral doses of 20 or 40 mg./kg. for 6 weeks. Results are expressed as micrograms per milliliter (mean ± *SE*). Levels in rats were determined by counting whole plasma; levels in dogs were measured by *Procedure A* (*Methods*) spectrophotometry.

Tissue Distribution—The distribution of radioactivity and apparent I in tissues of the rat 1 and 24 hr. after a single oral dose of I is shown in Table V. Only the stomach and small intestine showed levels of radioactivity greater than that in plasma after 1 hr. Since these measurements included the contents of each organ, the high levels present are undoubtedly associated, at least in part, with unabsorbed drug. However, the finding that only a fraction of the radioactivity present could be accounted for as apparent unchanged I (Table III) is of interest. This was true of most other tissues as well at 1 hr. after drug administration, except for plasma which contained a high percent of unchanged I. After 24 hr., tissue levels had declined markedly in most instances, but the fraction of apparent I present after 24 hr. was higher than at 1 hr. The decline in plasma levels was smaller than that observed in tissues.

Binding of I to nondiffusible constituents of human plasma was measured by equilibrium dialysis for 18 hr. at 37°. The drug was completely bound over a concentration range of 1–25 mcg./ml.

Localization in Inflamed Tissue—Concentrations of radioactive material were measured in normal and inflamed hind limbs of rats given labeled I as described in the *Methods* section. Inflamed tissue contained 5.5 ± 1.3 mcg./g. (mean ± *SE*) of radioactivity (expressed as I) compared to a concentration of 3.1 ± 0.6 mcg./g. in normal tissue. The difference was significant ($p < 0.05$) as shown by the paired *t*-test; levels in inflamed tissue were higher than those of control tissues in each of six rats studied.

Biliary Excretion—The excretion of radioactive material in the bile of the dog and rat after oral administration of labeled I is shown in Table VI. As shown, biliary excretion appeared to be highly dose dependent in the dog; 44% of a very low dose (0.02 mg./kg.) was recovered in the bile in 7 hr., whereas only 5% of a relatively high dose (120 mg./kg.) was thus excreted. About 19% of an intermediate dose (20 mg./kg.) was recovered in the bile, whereas 34% of a similar dose to rats (30 mg./kg.) was present in bile collected for 7 hr.

Table VI—Biliary Excretion of Radioactivity in the Dog and Rat after Oral Administration of I-^{14}C[a]

Hours	Dose Recovered, %			
	Dog A	Dog B	Dog C	Rat
1	4.8	4.9	0.0	4.1
2	7.6	7.0	0.6	4.8
3	7.1	5.3	2.0	5.6
4	10.2	1.8	0.7	6.1
5	4.5	0.2	0.6	5.2
6	5.3	0.2	1.3	4.6
7	4.4	—	—	3.9
1–7	43.9	19.4	5.2	34.3

[a] Drug was administered to Dog A in methylcellulose suspension (0.02 mg./kg.), to Dog B in saline–dimethylacetamide (20 mg./kg.), and to Dog C in capsule (120 mg./kg.). The rat received the drug in saline–dimethylacetamide (30 mg./kg.).

Metabolites of I—Analysis of urine of rats given I-^{14}C orally (25 mg./kg.) indicated that 30, 20, and 15% of the urinary radioactivity in the 0–24-hr., 24–48-hr., and 48–72-hr. samples were present as apparent unchanged I, respectively. Analysis of feces of rats given I-^{14}C orally or intravenously (3 mg./kg.) indicated that 50–95% of the fecal radioactivity was present as apparent unchanged I.

No labeled carbon dioxide was detected in the expired air of rats given I-^{14}C (3 mg./kg. i.v.), suggesting that the benzylidene bridge portion of the molecule was stable to further oxidation.

Bile of a dog given I-^{14}C orally (20 mg./kg.; 1–2-hr. sample) was examined for the presence of metabolites by TLC. Analysis of this bile sample for I showed that unchanged drug accounted for about 20% of the radioactivity in the sample. A 50-μl. aliquot was spotted on a silica gel plate and developed in chloroform–acetic acid (95:5). Two peaks were revealed on radiometric scanning, a major one at R_f 0.00 and a minor one at R_f 0.75. The R_f of authentic I in this system was 0.62.

Extraction with ethyl acetate of dog bile adjusted to pH 5 removed 82% of the radioactivity present. TLC of the ethyl acetate extract gave the results shown in Table VII.

Two radioactive peaks (three with Solvent B) were detected, one of which corresponded to unchanged I. In addition to scanning for radioactivity, plates developed in the five solvent systems were subjected to one or both of the following tests: (*a*) spraying with naphthoresorcinol (8), and (*b*) scraping off the radioactive metabolite area and testing for glucuronic acid (9). Control bile was also chromatographed and subjected to tests, with negative results in all cases.

Plates developed in the alkaline Solvent Systems B, C, and E gave a positive test on spraying with naphthorescorcinol, whereas plates developed in the acidic Solvent Systems A and D gave negative results. The blue spot produced, characteristic of glucuronic acid, had an R_f value similar to that of authentic glucuronic acid in the three solvents (0.14, 0.03, and 0.02, respectively, compared to 0.06, 0.66, and 0.08 for glucuronic acid). These results indicated

Table V—Tissue Distribution of Radioactivity after Oral Administration of I-^{14}C to Rats[a]

Tissue	^{14}C Levels			
	1 hr.		24 hr.	
	Total[b]	I[c]	Total[b]	I[c]
Liver	79 (62–95)	17 (16–18)	13 (12–14)	8 (3–12)
Lung	37 (36–38)	13 (12–14)	10 (10–10)	12 (8–15)
Heart	35 (34–36)	13 (10–16)	9 (8–9)	7 (5–8)
Testes	15 (14–16)	6 (4–8)	6 (5–6)	5 (5–5)
Spleen	18 (16–18)	6 (6–7)	4 (4–4)	2 (2–2)
Kidney	51 (48–54)	26 (24–27)	16 (14–17)	8 (6–9)
Stomach	509 (477–542)	156 (112–199)	20 (14–26)	6 (4–8)
Muscle	16 (14–18)	9 (8–10)	4 (3–4)	3 (2–4)
Fat	22 (17–27)	12 (10–15)	4 (4–6)	6 (4–7)
Small intestine	159 (127–191)	66 (36–96)	32 (26–33)	20 (14–27)
Brain	9 (8–10)	4 (4–4)	2 (2–2)	2 (2–2)
Red cells	44 (40–49)	15 (12–18)	4 (3–4)	5 (3–6)
Plasma	134 (132–137)	107 (104–110)	52 (51–53)	34 (34–35)

[a] Average and range for two rats at each time interval; dose was 32 mg./kg. p.o. [b] Total radioactivity, expressed as micrograms of I per gram tissue. [c] Apparent I, isolated as described in *Methods*, *Procedure A*. Values are corrected for recovery obtained with each tissue and expressed as micrograms per gram tissue.

Table VII—TLC of Bile of Dog Given I-^{14}C (20 mg./kg.) Orally[a]

Sample	R_f Solvent A	Solvent B	Solvent C	Solvent D	Solvent E
Bile	0.00; 0.58	0.48; 0.57; 0.89	0.68; 0.45	0.74; 0.23	0.0; 0.33
I	0.58	0.55	0.54	0.71	0.26

[a] The solvent systems used were as follows: A, chloroform–acetic acid (95:5); B, ethyl acetate–isopropyl alcohol–20% ammonia (5:4:3); C, isopropyl alcohol–15 *N* ammonia (8:2); D, isopropyl alcohol–acetic acid (95:5); and E, *n*-butanol saturated with ammonia.

that glucuronic acid was released from the metabolite on exposure to alkali.

The metabolite spots at R_f 0.00 and 0.23 in Solvents A and D, respectively, were scraped into 0.1 *N* NaOH and kept for 10 min. at room temperature. The mixture now gave a positive test for glucuronic acid by the second method.

In addition, the metabolite present in dog bile was shown to be converted to I on exposure to dilute alkali in the following experiment. Bile (0.2 ml.) from a dog given 20 mg./kg. of I (Table VI) was added to 0.8 ml. of 0.1 *N* NaOH, and the solution was kept at room temperature for 10 min. The sample was then acidified and assayed for I as described in the *Methods* section. Samples not treated with base were assayed concurrently. The results showed that the percent of apparent I in the bile increased markedly after exposure to the base in all samples, except the 1-hr. sample which apparently contained mainly unchanged I. The fraction of the total radioactivity present represented by I increased from 24 to 94% in the 2-hr. sample, from 19 to 90% in the 3-hr. sample, from 28 to 71% in the 4-hr. sample, and 53 to 93% in the 6-hr. sample.

Likewise, bile exposed to dilute alkali (2-hr. sample) gave only one radioactive peak, at R_f 0.63, when subjected to TLC in Solvent A, which corresponded in R_f value to I (R_f 0.66). The radioactive peak at R_f 0.00 (Table VII) was no longer observed.

DISCUSSION

The title compound, an indene isostere of indomethacin, was well absorbed after oral administration to the rat, excretion patterns after oral and intravenous doses being nearly identical. Drug was detected in plasma 0.5–1 hr. after oral administration and reached maximal levels at 1–2 hr. Absorption appeared to be more prolonged after administration of higher doses to rats.

Plasma half-lives of 4.5 and 1–2 hr. in the rat and dog indicated that I was metabolized more rapidly in the dog. The drug was widely distributed throughout rat tissues.

A large fraction of either an oral or intravenous dose of I was excreted in the feces of rats and dogs. Biliary excretion of the compound was extensive and appeared to be inversely proportional to the dose; saturation of the biliary excretion mechanism is possible (10, 11). The acyl glucuronide of I was apparently a major metabolite of the drug in dog bile. I was not localized to a significant extent in inflamed tissues of rats.

Comparison of the results reported here for I with those previously reported for indomethacin (12) permits estimation of the effect of: (*a*) substitution of an indene nucleus for the indole, and (*b*) substitution of an easily hydrolyzed *N*-acyl group by a stable benzylidene group. Indomethacin was extensively hydrolyzed in the rat (13) but excreted intact as the acyl glucuronide in the dog (12).

The excretion pattern was markedly different in the rat for the two compounds, with a much greater fraction of the dose being eliminated in feces with I than with indomethacin. In the dog, however, the excretion pattern for both compounds was similar, a high percent being eliminated in feces.

The plasma half-life of I after an intravenous dose to rats was 4.5 hr., the same as that of indomethacin. Apparently, the two compounds were metabolized at the same rate in this species. *O*-Demethylation is a possible metabolic pathway used for both I and indomethacin.

Neither drug was found to be concentrated in rat tissues but both were widely distributed. The indene analog appeared to be less extensively excreted in dog bile than indomethacin when the comparison was made at equivalent dose levels. Excretion in rat bile was nearly equivalent for I and indomethacin.[8]

A major metabolite of both compounds in dog bile was the corresponding acyl glucuronide, indicating that the indolyl and indenylacetic acid moieties are readily conjugated with glucuronic acid.

I was localized to a significant extent in inflamed tissue of rats. Such localization was reported for several other compounds (14–16); indomethacin has also been shown to be localized significantly in inflamed tissue of rats[8].

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[8] Unpublished data of the authors.