On the basis of the results reported here, one may speculate that contamination, emanating from outside the containers, can be the result of poor handling techniques. It may further be concluded that under the stress conditions studied, fully capped Type A containers were contaminated to a greater extent than those of Types B and C. It was also observed that with the containers partially uncapped, Types A and B were contaminated more frequently than was Type C. Furthermore, there was no difference between contamination rates for the control units.

It is the recommendation of the authors that regardless of the type of container used, or the precautions and engineering by the manufacturer, it is imperative that aseptic techniques be employed from the time the container is removed from the carton to the time infusion is completed.

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2-(Aminoethanesulfonylamino)thiazole and Related Compounds I: Stability, Absorption, Excretion, and Some Pharmacological Activities

SHUN-ICHI NAITO▲ and SAKAE SHIMIZU

Abstract □ Decomposition rate constants of nicotinoyltauraminothiazole in aqueous solution at high temperatures were determined. Unchanged nicotinoyltauraminothiazole and three decomposition products (tauraminothiazole, aminothiazole, and an unknown substance) were detected by TLC. Nicotinoyltauraminothiazole has both analgesic and anti-inflammatory activities. Blood levels, tissue distribution, and excretion of nicotinoyltauraminothiazole in animals were also investigated. In urine of rabbits after the administration of the chemical, unchanged compound, tauraminothiazole, and a metabolite of undetermined structure were isolated.

Keyphrases □ Nicotinoyltauraminothiazole—stability and biopharmaceutical studies □ 2-(Aminoethanesulfonylamino)thiazoles—stability and biopharmaceutical studies, nicotinoyltauraminothiazole □ Anti-inflammatory activity—nicotinoyltauraminothiazole

Only a few thiazole derivatives are marketed drugs. These include dithiazanine iodide (anthelmintic) (1), succinylsulfathiazole (sulfonamide) (2), sulfathiazole (sulfonamide) (3), thiabendazole (anthelmintic) (4), and thiamine derivatives (vitamin).

Although tauraminothiazole [2-(aminoethanesulfonylamino)thiazole] was synthesized by Winterbottom *et al.* (5), nicotinoyltauraminothiazole is a new compound and was synthesized in a series of 2-aminoethanesulfonic acid derivatives (6–8). If taurine is liberated partially from nicotinoyltauraminothiazole *in vivo*, the surface activity of taurine must have some effect on the activity of the remaining components (2-aminothiazole and/or unchanged nicotinoyltauraminothiazole). It was established that the bond between the amino group and the 2-aminoethanesulfonyl group cannot be ruptured easily in rabbits; liberation of taurine from the nicotinoyltauraminothiazole will be examined later in man.

In the present work, the stability, acute toxicity, and some pharmacological activities of nicotinoyltauraminothiazole were investigated. Its absorption, excretion, distribution, and metabolic pathway were also studied.

EXPERIMENTAL

Sample for Kinetic Study of Stability—About 1 ml. of a 0.8% nicotinoyltauraminothiazole hydrochloride solution was placed in a colorless ampul (1-ml. capacity). The samples were stored at 50, 60, and 70 ± 1°, and the solutions were assayed at various times.

Determination of Nicotinoyltauraminothiazole in Aqueous Solution—Five microliters of the sample solution was spotted on TLC plates, and the plates were developed for a 15-cm. distance using a mixture of butanol–dioxane–chloroform–28% ammonia (8:2:1:1) as a developing solvent and diatomite (Kieselgel G) as the adsorbent. Zones were scraped off the glass plate 1 cm. above and below the original point and were extracted with 3 ml. of water on a boiling water bath for 3 min. After centrifugation, a mixture of 2 ml. of the supernate and 1 ml. of 10% cyanogen bromide solution was allowed to stand for 20 min. at room temperature and then 0.2 ml. of 10% *p*-aminoacetophenone solution was added. After 10 min., 4 ml. of *n*-butanol was added to the mixture and this mixture was shaken for 5 min. The mixture was kept in a dark place for 10 min., and the absorbance of the butanol layer (the supernate) after centrifugation was measured at 450 nm. The absorbances were corrected by subtracting a blank value.

Acute Toxicity in Mice—The experiment was designed in the same way as described previously (6). Nicotinoyltauraminothiazole, its hydrochloride, 2-aminothiazole, or tauraminothiazole hydrochloride as aqueous solutions was administered to mice. The volume of the test sample solutions was adjusted to keep it constant at 0.1 ml./10 g. body weight. The LD_{50} of the chemical was calculated from the number of animals that died during the next 72 hr., according to the method of Litchfield and Wilcoxon (9).

Effect of Nicotinoyltauraminothiazole on Squirming and Capillary Permeability—Male dd strain mice, weighing 20 ± 1 g., were given the test compound orally. The experiment was carried out using the method described previously (6).

Tail Withdrawal Reflex in Mice—The same method as the analgesimetry described in the paper of Ben-Bassat *et al.* (10) was used. Each group consisted of 10 male mice (dd strain, average weight 16 g.).

Anti-Inflammatory Activity—Inflammation was produced by injection of carrageenin (0.1 ml. of 2% suspension) into the plantar surface of the hind paw of male rats (Wistar strain, average weight 230 g.). The method described in a previous paper (7) was used.

Inflammation was also produced by injection of serotonin (0.1 ml. of 0.0025% aqueous solution) into the plantar surface of the hind paw of male rats (Wistar strain, average weight 150 g.). Normal saline solution was injected into the other hind paw as a control. The test compound was administered subcutaneously in an aqueous solution or suspension whose volume was kept constant at 0.5 ml./100 g. body weight. The test compound was administered 30 min. before injection of the phlogistic agent. Control animals received an injection of the vehicle, and each group consisted of five rats. The effect of the test compound on the edema was determined volumetrically 1 hr. after injection of the phlogistic agent. The experimental conditions reported by Theobald and Domenjoz (11) were used.

Anaphylactic Shock in Guinea Pigs—Female guinea pigs (Hartley strain), with a body weight of about 320 g., were used in the experiment following the procedure of Labelle and Tislow (12). Guinea pigs were challenged exactly 0.5 or 1 hr. after drug administration by rapid injection of 1 ml. of horse serum into the saphenous vein.

Antihistamine Activity—Female guinea pigs (Hartley strain, average weight 360 g.) were used in the histamine tests. The compound was administered subcutaneously 0.5 and 1 hr. before histamine injection.

Histamine dihydrochloride was injected rapidly into the saphenous vein in a dosage of 1.1 mg./kg. The test was made in fasted animals.

Antipyretic Activity—To male rabbits weighing 2.7 kg., 15 mcg./kg. of nonanaphylactogenic polysaccharides obtained from *Pseudomonas fluorescens*[1] was administered intravenously, and nicotinoyltauraminothiazole solution was given subcutaneously 2 hr. after the administration of the pyrogen solution. Body temperature was recorded every 15 min. for 6 hr. Each group consisted of three rabbits.

Detection of Metabolites of Nicotinoyltauraminothiazole in Blood—A mixture of 1 ml. of water, 0.8 g. of sodium chloride, and 7 ml. of ethyl acetate was added to 1 ml. of plasma taken 1 hr. (time of peak blood level) after ingestion of 350 mg./kg. of nicotinoyltauraminothiazole. This mixture was shaken vigorously for 30 min. After centrifugation for 5 min., 4 ml. of the ethyl acetate layer was evaporated to dryness on a boiling water bath, and the residue was dissolved in 50 μl. of water. Ten microliters of this solution was spotted on a chromatographic plate for TLC. A blood sample gathered prior to ingestion of the chemical was treated by the same procedure as a control.

For TLC, the solvent system was ethanol–chloroform–28% ammonia (8:2:1), the adsorbent was diatomite (Kieselgel G), and the color developer was modified Folin reagent (13). One spot having an R_f value of 0.76 (blue) was observed in treated plasma; no spots were observed in control plasma. The R_f value of nicotinoyltauraminothiazole was 0.76 (blue).

Determination of Nicotinoyltauraminothiazole in Plasma—A mixture of 1 ml. of plasma and 1 ml. of 10% cyanogen bromide solution was treated by the procedure described under *Determination of Nicotinoyltauraminothiazole in Aqueous Solution.* A mixture of 0.9 ml. of untreated (normal) animal plasma and 0.1 ml. of nicotinoyltauraminothiazole solution of known concentration was treated as above to prepare a calibration curve. The procedure described is a modification of the method reported by Harris and Raymond (14).

Determination of Nicotinoyltauraminothiazole in Rat Bile—Male rats (Wistar strain, body weight 150–170 g.) were treated by the method described previously (15). Each group consisted of five rats.

Following oral administration of 200 mg./kg. of nicotinoyltauraminothiazole by a stomach tube, 1 ml. of bile (instead of plasma) was treated according to the method for determination of nicotinoyltauraminothiazole in blood.

Distribution of Nicotinoyltauraminothiazole in Rat Organs—To male rats (Wistar strain, body weight 150 ± 10 g.), 200 mg./kg. of nicotinoyltauraminothiazole was administered orally and the animals were killed either 1 hr. (time of peak blood level) or 24 hr. following administration. Each group consisted of five rats. Six organs (heart, lungs, spleen, kidneys, brain, and liver) were assayed for nicotinoyltauraminothiazole. After bleeding each rat, each organ was separated and homogenized with 4 ml. of water for the brain, 10 ml. of water for the liver, and 3 ml. of water for the heart, lungs, spleen, or kidneys. After centrifugation, 1 ml. of the supernate of each homogenate was used for the assay, which was performed as described under *Determination of Nicotinoyltauraminothiazole in Aqueous Solution.*

Separation of Metabolites of Nicotinoyltauraminothiazole in Rabbits—Urine from three female rabbits (average weight 3.0 kg.), following ingestion of 200 mg./kg. of nicotinoyltauraminothiazole, was submitted to lyophilization. This residue was designated as A. The residue of urine obtained from three rabbits who did not receive the drug was designated as B and served as a control.

A mixture of 100 mg. of Residue A or B and 1 ml. of 5 *N* HCl was kept in an incubator at 37 ± 2° for 1 hr. After the addition of 1 ml. of 5 *N* Na_2CO_3 solution, the mixture A′ from A or B′ from B was submitted to TLC. Also, a mixture of 2 ml. of water and 100 mg. of Residue A or B was submitted to TLC. No difference was observed in the number of spots between Residue A and A′ or between Residue B and B′.

Assay of Metabolites of Nicotinoyltauraminothiazole in Rabbit Urine—*Determination of Nicotinoyltauraminothiazole*—A mixture of 1 ml. of water and 20 mg. of the lyophilized residue of urine from rabbits (average weight 3.0 kg.) who had received 200 mg./kg. of nicotinoyltauraminothiazole was centrifuged, and 10 μl. of the supernate was submitted to TLC, using a mixed solvent of butanol–dioxane–methylene chloride–28% ammonia (8:2:1:2). The spot corresponding to nicotinoyltauraminothiazole was scraped off the TLC plate and extracted for 3 min. with 3 ml. of water on a boiling water bath. Two milliliters of the centrifugation supernate was treated by the same procedure as described under *Determination of Nicotinoyltauraminothiazole in Aqueous Solution.*

Determination of Tauraminothiazole—Ten microliters of the supernate obtained by the same procedure as was used above was submitted to paper chromatography (PC), using a mixed solvent of ethanol–chloroform–28% ammonia (5:1:1) and filter paper[2]. The spot corresponding to tauraminothiazole was cut out and extracted for 3 min. with 3 ml. of water on a boiling water bath. To determine the concentration of tauraminothiazole, 1 ml. of the centrifugation supernate was treated with 0.4% ferricyanide and 1% $Fe(NO_3)_3$ in 0.7 *N* HNO_3 (13).

Determination of Unknown Metabolite (Metabolite I)—A mixture

[1] T. T. G. No. 1, Fujisawa Yakuhin Kogyo Co., Osaka, Japan.

[2] No. 50, Toyo Roshi Co., Osaka, Japan.

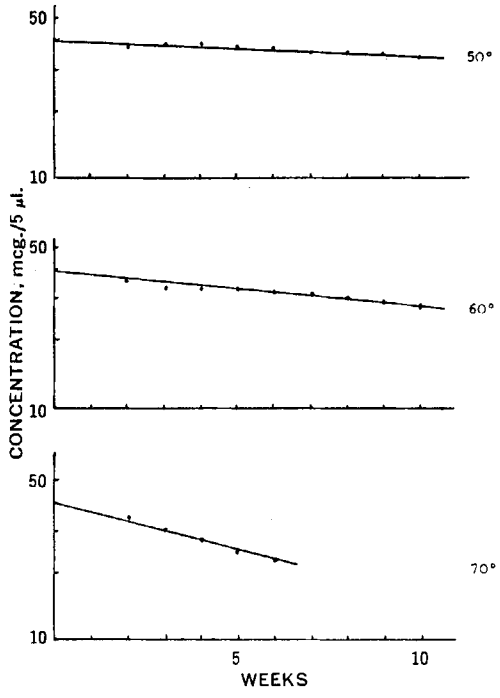

Figure 1—*Concentration of nicotinoyltauraminothiazole in aqueous solution as its hydrochloride.*

of 50 mg. of the lyophilized residue of urine and 0.5 ml. of 1 *N* NaOH was heated for 100 min. on a boiling water bath. This mixture was combined with 0.5 ml. of 1 *N* HCl and was then made alkaline with 0.1 ml. of 5 *N* Na_2CO_3 solution. The mixture thus obtained was made up to 1 ml. with water and analyzed according to the method for tauraminothiazole. Tauraminothiazole must be liberated from nicotinoyltauraminothiazole and Metabolite 1 in urine by alkali hydrolyzation. Therefore, tauraminothiazole liberated from Metabolite 1 can be calculated by subtracting both the amount of tauraminothiazole that existed originally and the amount of tauraminothiazole equivalent to nicotinoyltauraminothiazole

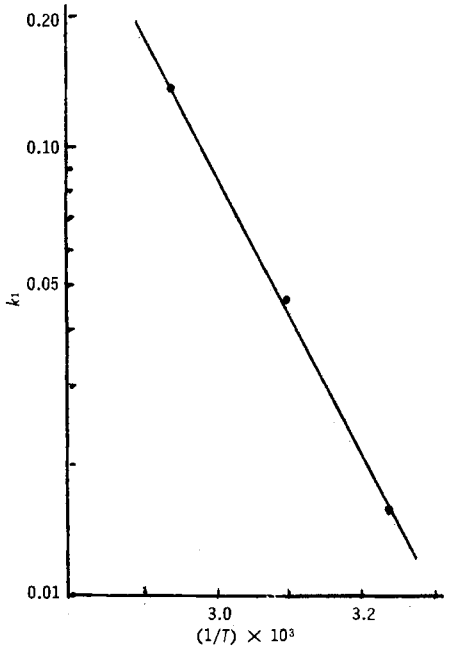

Figure 2—*Arrhenius plot of decomposition rate constants of nicotinoyltauraminothiazole hydrochloride in aqueous solution. Key:* T, *absolute temperature; and* k_1, *decomposition rate constant in reciprocal days.*

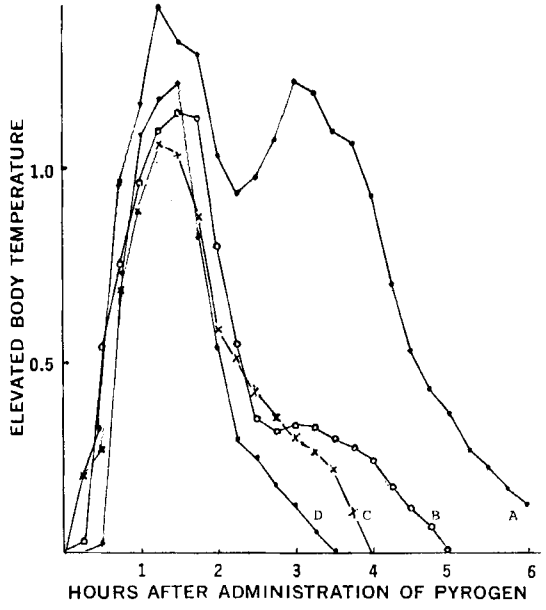

Figure 3—*Mean curve for the fall of elevated body temperature of male rabbits receiving pyrogen. Each group consisted of three rabbits. Key: A, control group, mean basal body temperature (MBBT) 39.1°; B, 75 mg./kg. of nicotinoyltauraminothiazole, MBBT 39.2°; C, 100 mg./kg. of nicotinoyltauraminothiazole, MBBT 39.2°; and D, 150 mg./kg. of nicotinoyltauraminothiazole, MBBT 39.3°.*

in urine from the total tauraminothiazole obtained by alkali hydrolyzation of the lyophilized residue of urine.

Identification of Tauraminothiazole Obtained by Hydrolyzation of Metabolite 1—In the procedure under *Determination of Nicotinoyltauraminothiazole in Rabbit Urine*, 10 spots corresponding to Metabolite 1 were scraped off the TLC plate and extracted for 1 min. with 10 ml. of ethyl acetate on a boiling water bath. Following evaporation of the solvent, the residue was mixed with 0.5 ml. of 1 *N* NaOH and heated for 100 min. on a boiling water bath. The mixture was mixed with 0.5 ml. of 1 *N* HCl and then made alkaline with 0.1 ml. of 5 *N* Na_2CO_3 solution. This mixture was extracted with 3 ml. of ethyl acetate, and the residue obtained after evaporation of the ethyl acetate layer was dissolved in a small amount of ethyl acetate and chromatographed (TLC), using a mixed solvent of butanol–dioxane–methylene chloride–28% ammonia (8:2:1:2). The spot corresponding to tauraminothiazole was scraped off the TLC plate and extracted with a small amount of ethyl acetate. The solvent was removed and the residue was submitted to a mixed micromelting-point determination with the authentic sample.

RESULTS AND DISCUSSION

TLC of the extract from stability samples of nicotinoyltauraminothiazole hydrochloride (10 weeks at 70 ± 1°) produced four spots when a mixed solvent of butanol–dioxane–chloroform–28% ammonia (8:2:1:1) was used. The R_f values of the four spots corresponding to 2-aminothiazole, tauraminothiazole, unchanged nicotinoyltauraminothiazole, and an unknown decomposition product were 0.78, 0.23, 0, and 0.41, respectively. These spots were detected as a blue color by use of modified Folin reagent (13). The assay results (Fig. 1) of the unchanged nicotinoyltauraminothiazole indicate that degradation of nicotinoyltauraminothiazole hydrochloride obeyed first-order kinetics. Constants (16) concerning the stability of nicotinoyltauraminothiazole hydrochloride were as follows: decomposition rate constant (k_1 in reciprocal days) at 50°, 0.00154; k_1 at 60°, 0.00473; k_1 at 70°, 0.01337; heat of activation, 23.6 kcal./mole/°; and log frequency factor, 13.7. The Arrhenius plot of the rate constants was linear (Fig. 2). The predicted concentration after 2 years at 25° is 83.3%. Therefore, it is assumed that nicotinoyltauraminothiazole is fairly stable in aqueous solution at room temperature.

The LD_{50}'s of 2-aminothiazole, tauraminothiazole hydrochloride, nicotinoyltauraminothiazole, and its hydrochloride by intraperitoneal administration to mice were 940 (866–1020), 780 (719–846),

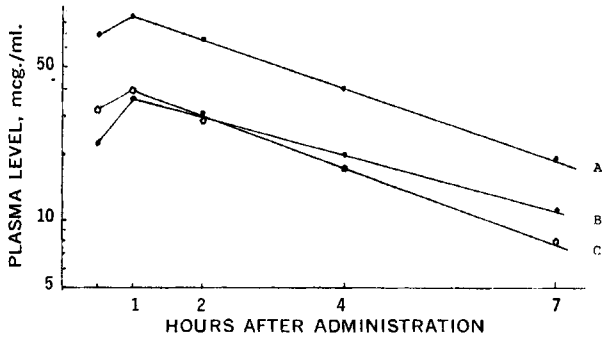

Figure 4—*Mean plasma level of nicotinoyltauraminothiazole after oral administration to three male rabbits (average weight 3.0 kg.) at different doses. Key: A, 200 mg./kg.; B, 150 mg./kg.; and C, 100 mg./kg.*

1280 (1143–1534), and 940 (797–1109) mg./kg., respectively (with 95% confidence limits). No significant difference was observed in the LD_{50}'s between male and female mice. Although the animals receiving intraperitoneal doses below 800 mg./kg. of nicotinoyltauraminothiazole exhibited no behavioral abnormality, the intraperitoneal dose of 4000 mg./kg. produced a transient ataxic walk with extended hind limbs. After a longer period, the animal showed lacrimation, piloerection, and convulsions; all of the animals died from respiratory failure at the 4000-mg./kg. dose.

The purpose of squirming and permeability tests was to obtain information concerning the concurrent changes in the peritoneal capillary permeability during squirming through the method of Whittle (17). The ED_{50} of nicotinoyltauraminothiazole for inhibition of squirming was 200 (165–242) mg./kg., and this chemical did not change the permeability response compared with that of the control group.

With respect to the tail withdrawal reflex in mice (10), computation of the ED_{50} and its confidence limits was made by probit analysis. This was done by dichotomizing the reactions after 30 min. into two groups: "refractory," *i.e.*, pain reaction time of 2.0 sec. or more, and "nonrefractory" for aminopyrine and nicotinoyltauraminothiazole. The ED_{50}'s and 95% confidence limits were 48 (35–66) mg./kg. for aminopyrine and 225 (186–272) mg./kg. for nicotinoyltauraminothiazole. The analgesic activity of nicotinoyltauraminothiazole seems to be less than that of aminopyrine, according to the ED_{50}'s of the tail withdrawal reflex in mice.

The ED_{50}'s (with 95% confidence limits) of nicotinoyltauraminothiazole on edema induced by carrageenin and serotonin were 185 (112–305) and 43.5 (27.2–69.6) mg./kg., respectively. The ED_{50} of sodium salicylate for edema induced by serotonin was 370 (203–666) mg./kg., and this drug had no effect on carrageenin-induced edema at doses lower than 500 mg./kg. These results show that nicotinoyltauraminothiazole has fairly potent anti-inflammatory activity which compares with that of sodium salicylate.

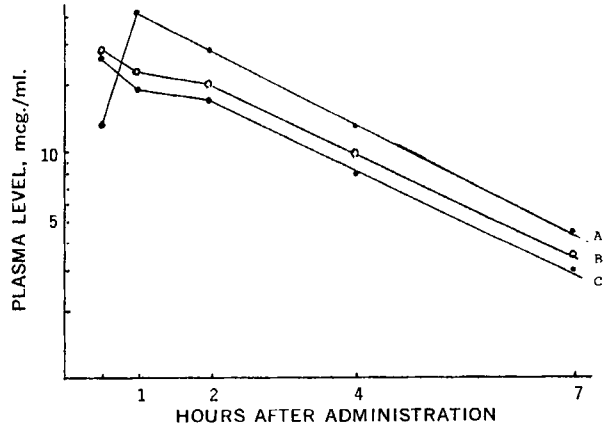

Figure 5—*Mean plasma level of nicotinoyltauraminothiazole after oral administration to male rats (Wistar strain, average weight 130 g.) at different doses. Each group consisted of five rats. Key: A, 200 mg./kg.; B, 150 mg./kg.; and C, 100 mg./kg.*

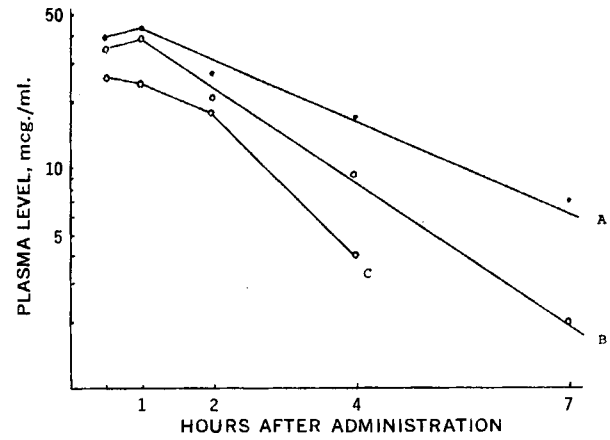

Figure 6—*Mean plasma level of nicotinoyltauraminothiazole after oral administration to male mice (dd strain, average weight 17 g.) at different doses. Each group consisted of 10 mice. Key: A, 200 mg./kg.; B, 150 mg./kg.; and C, 100 mg./kg.*

Antihistaminic and antianaphylactic shock activities of nicotinoyltauraminothiazole were evaluated by the method of Labelle and Tislow (12). No difference in antihistaminic activity was observed between 200- and 300-mg./kg. doses of nicotinoyltauraminothiazole when the compound was administered subcutaneously 0.5 hr. before histamine injection. Forty percent of 10 guinea pigs survived in each group. When the compound was given subcutaneously 1 hr. before histamine injection, only 20% of 10 guinea pigs survived. Therefore, the antihistaminic activity seems to be greater when the chemical is given 30 min. rather than 1 hr. before histamine injection. Antihistaminic activity of the chemical was not investigated in detail because of its low activity.

Three out of 10 guinea pigs, who received 200 mg./kg. of nicotinoyltauraminothiazole, survived the first 10 min. following the horse serum injection. When 100 or 300 mg./kg. of nicotinoyltauraminothiazole was given, two out of 10 guinea pigs survived. These results indicate that the antianaphylactic activity of this compound is weak.

Results of antipyretic activity tests are presented in Fig. 3. Nicotinoyltauraminothiazole, at doses of 100 and 150 mg./kg., gradually decreased the elevated body temperature of all rabbits used.

Before performing quantitative determinations of nicotinoyltauraminothiazole in blood, it was ascertained by TLC that there are no metabolites of the chemical detectable in blood. Semilogarithmic plots of blood level *versus* time are shown in Figs. 4–6. A semilogarithmic plot of mean plasma level of nicotinoyltauraminothiazole after intravenous administration of 33 mg./kg. to rabbits is presented in Fig. 7. For the latter experiment, the compound was dissolved in a mixed solution of 0.5 ml. of 5 *N* HCl and 15.5 ml. of 0.9% normal saline solution to make a 2% solution of the compound (pH 2.0).

Collection of bile from rats under continuous urethan anesthesia indicated that nicotinoyltauraminothiazole has no effect upon bile

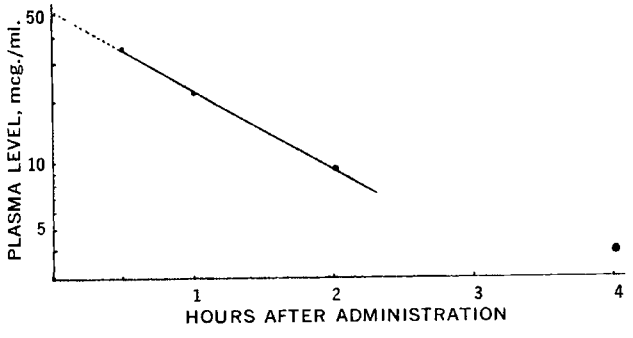

Figure 7—*Mean plasma level of nicotinoyltauraminothiazole after intravenous administration to male rabbits (average weight 3.0 kg.) at 33-mg./kg. dose.*

Table I—TLC of Lyophilized Urine of Rabbits and Rat Bile[a]

Sample[b]	Solvent[c]	R_f[d] (Substance Assumed)
2-Aminothiazole (I)	A	0.85
Tauraminothiazole (II)	A	0.10
Nicotinoyltaura-minothiazole (III)	A	0.41
Residue A	A	0.47
		0.41 (III)
		0.36 (Metabolite 1)
		0.17
		0.10 (II)
Residue B	A	0.47
		0.17
Mixture A′	A	0.47
		0.41 (III)
		0.36 (Metabolite 1)
		0.17
		0.10 (II)
2-Aminothiazole	B	0.81
Tauramino-thiazole	B	0.29
Nicotinoyltaura-minothiazole	B	0.53
Residue A	B	0.53 (III)
		0.43 (Metabolite 1)
		0.29 (II)
		0.23
Residue B	B	0.23
Tauramino-thiazole	C	0.24
Nicotinoyltaura-minothiazole	C	0.54
Hydrolyzed Residue A	C	0.54 (III)
		0.24 (II)
		0.18
Hydrolyzed Residue B	C	0.18
Residue A	C	0.54 (III)
		0.43 (Metabolite 1)
		0.24 (II)
		0.18
Residue B	C	0.18
Rat bile A	C	0.54 (III)
Rat bile B	C	Nil
Nicotinoyltaura-minothiazole	D	0.87
Tauramino-thiazole	D	0.43
Hydrolyzed Residue A	D	0.87 (III)
		0.55
		0.43 (II)
		0.35
		0.15
Hydrolyzed Residue B	D	0.55
		0.35
		0.15
Residue A	D	0.87 (III)
		0.80 (Metabolite 1)
		0.55
		0.43 (II)
		0.35
		0.15
Residue B	D	0.55
		0.35
		0.15
Rat bile A	D	0.87 (III)
Rat bile B	D	Nil

[a] The adsorbent was diatomite (Kieselgel G), 0.25 mm. in thickness. The color developer was modified Folin reagent, and the developed distance was 15 cm. [b] Residues A and B were described in the *Experimental* section. Hydrolyzed Residues A and B were composed of mixtures of 50 mg. of Residue A or B and 0.5 ml. of 1 *N* NaOH solution heated for 100 min. on a boiling water bath. The reaction mixture was neutralized with 1 *N* HCl and made slightly alkaline with sodium carbonate. This mixture was used for TLC. Mixtures A′ and B′ were described in the *Experimental* section. Rat bile A was bile collected for 7.5 hr. following oral administration of 200 mg./kg. of nicotinoyltauraminothiazole to rats. Three milliliters of bile was extracted with 7 ml. of ethyl acetate, the solvent was removed, and the residue was dissolved in 50 μl. of ethyl acetate. Ten microliters of the ethyl acetate solution was spotted on a TLC plate. Rat bile B was bile collected from rats receiving no compound and was treated by the same procedure as in the case of rat bile A. [c] Solvent systems were: A, butanol–dioxane–methylene chloride–28% ammonia (8:2:1:1); B, butanol–dioxane–methylene chloride–28% ammonia (8:2:1:3); C, butanol–dioxane–methylene chloride–28% ammonia (8:2:1:2); and D, ethanol–chloroform–28% ammonia (4:1:1). [d] Color of all spots was blue or light blue.

flow and total bile volume excreted in 7.5 hr., as compared with untreated control rats. The residue from ethyl acetate extraction of rat bile contained no metabolites when nicotinoyltauraminothiazole was administered orally. This fact was supported by the TLC data shown in Table I (Solvents C and D). The concentration of nicotinoyltauraminothiazole in rat bile, excreted for 7.5 hr. following oral administration of a 200-mg./kg. dose, was 375 ± 48 mcg./kg. (mean value of five rats and standard error).

Tissue levels of nicotinoyltauraminothiazole in rat organs 1 hr. after oral administration to five rats were 5.6 ± 0.9 in the brain, 23.1 ± 2.3 in the heart, 30.3 ± 5.5 in the lungs, 20.4 ± 3.3 in the liver, 36.3 ± 3.2 in the spleen, and 44.3 ± 7.2 mcg./g. in the kidneys (mean values ± standard errors). Nicotinoyltauraminothiazole concentrations in all rat organs were below the assay sensitivity 24 hr. following administration.

Metabolites of nicotinoyltauraminothiazole were examined in the lyophilized residue of rabbit urine after oral administration of 200 mg./kg. of the chemical to three rabbits. When the lyophilized residue was submitted to TLC, three spots [unchanged nicotinoyltauraminothiazole, tauraminothiazole, and an unknown metabolite (Metabolite 1)] were detected. Two of the three metabolites, nicotinoyltauraminothiazole and tauraminothiazole, were identified by mixed micromelting-point determination with the respective authentic samples. The chemical structure of Metabolite 1 has not been established, but tauraminothiazole was obtained when Metabolite 1 was treated with 1 *N* NaOH on a boiling water bath. On the other hand, it was known by TLC that tauraminothiazole cannot be liberated from Metabolite 1 after incubation with 5 *N* HCl at 37 ± 1° for 1 hr. The structure of Metabolite 1 will be investigated.

The results of quantitative determination of the metabolites in rabbit urine suggested that 8.7% of the compound administered orally is excreted as nicotinoyltauraminothiazole, 64.1% is excreted as tauraminothiazole, and 17.1% is excreted as Metabolite 1. Total recovery was 89.9% of the dose, indicating excellent absorption of nicotinoyltauraminothiazole in rabbits. It was also ascertained by TLC that all of the detectable metabolites were excreted within 48 hr. The ring system of sulfathiazole is known to be stable *in vivo*, but 2-aminothiazole, an antithyroid agent, was reported to be rapidly destroyed in the body (18). In the case of nicotinoyltauraminothiazole, the ring system seems to be fairly stable *in vivo*.

SUMMARY

1. Nicotinoyltauraminothiazole in aqueous solution is fairly stable at room temperature.

2. Analgesic, antihistaminic, antianaphylactic, and antipyretic activities of nicotinoyltauraminothiazole seem to be relatively low. However, the activity of this compound is about eight times higher than that of sodium salicylate on edema induced by serotonin.

3. About 90% of the dose was excreted in urine as drug plus metabolites after oral administration of nicotinoyltauraminothiazole to rabbits.

4. Nicotinoyltauraminothiazole may be an interesting compound for clinical trials because of its low toxicity, good absorbability, and potent anti-inflammatory activity.

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Evaluation of Interactions between Polymers and Low Molecular Weight Compounds by GLC I: Methodology and Interaction Evaluation

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Abstract □ Sorption–desorption thermodynamics were evaluated for two polymers and 13 low molecular weight compounds. The polymers, polyethylene and polyvinyl chloride, are of major use in packaging. The sorbents were bacteriostatic agents of pharmaceutical utility and organic solvents employed in package fabrication. GLC procedures were used where the polymers constituted the stationary phases and the sorbents constituted the mobile phases of the columns. Auxiliary methods were adapted for obtaining the data necessary for the thermodynamic computations. The measurement of interaction affinities was based on Raoult's law activity coefficients. The GLC methodology was fast and convenient to perform and could be a valuable tool for applied and theoretical investigations in this area.

Keyphrases □ Polymer–low molecular weight compound interactions—sorption–desorption thermodynamic methodology, GLC □ Sorption–desorption thermodynamic methodology—polyethylene and polyvinyl chloride, 13 low molecular weight compounds, GLC □ Package–content interactions—polymers and low molecular weight compounds, GLC method for evaluating sorption–desorption thermodynamics □ Plastics—interactions of packaging materials with low molecular weight compounds evaluated by GLC, sorption–desorption thermodynamics □ GLC—evaluation of polymer–low molecular weight compound interactions, sorption–desorption thermodynamic methodology

The use of polymers in packaging may result in sorption of ingredients from the contents or desorption of compounds used in package fabrication. These processes may render a product unsuited for use. The phenomena result from interactions between the polymer and the low molecular weight compound and diffusion. The thermodynamics of the interaction determine the equilibrium amount of sorbent in the polymer, and diffusion affects the rate for attaining the equilibrium. The available information on such interactions is insufficient for optimum use of polymers in packaging; thus the objectives of this work were to evaluate the interaction thermodynamics and to use the quantities obtained for relative grading of affinities and toward a better understanding of the systems. Since conventional methods for these objectives are cumbersome and time consuming, GLC procedures were adapted by using the polymers as the stationary phases and the low molecular weight compounds as the mobile phases of the columns.

GLC BACKGROUND

The retention of a compound in a GLC column is a function of its saturation vapor pressure at the column temperature and the energy of interaction with the stationary phase. The specific retention volume, V_g^0, is characteristic for a given mobile–stationary phase system and is derived from experimental quantities through (1):

$$V_g^0 = \frac{(t_r - t_a)\dot{V}j}{W_1}\frac{273}{T} \qquad \text{(Eq. 1)}$$

where t_r is the retention time for the compound, t_a is the injection pulse, $\dot{V}$ is the corrected inert gas flow rate, j is the compressibility