is $F_{PH}F_H$, where F_{PH} is the fraction of the dose reaching the liver as intact drug and F_H is the fraction of the drug reaching the liver intact that enters the systemic circulation in unmetabolized form. If $F_{PH} = F$ after portacaval shunt (assuming that F_{PH} was not affected by the surgery and that there was no significant development of collateral circulation after the surgery), then F_H before surgery was 0.253/0.542 or 0.47 (based on the average systemic availability values from Table III). Thus, the prehepatic and hepatic first-pass effects on propoxyphene appear to be of similar magnitude in the dog.

Hepatic cirrhosis often is associated with the formation of portacaval shunts and reduction of drug-metabolizing enzyme activity (23, 24). These changes should increase the systemic availability of a drug with the pharmacokinetic characteristics of propoxyphene. This increase should be less pronounced if a substantial part of the first-pass effect is due to prehepatic biotransformation, provided that liver disease does not affect the prehepatic metabolism of propoxyphene. Unfortunately, the effect of liver disease on the prehepatic biotransformation of drugs is not known. However, it appears prudent to reduce the dosage of propoxyphene in patients with portacaval shunt or with cirrhosis of the liver.

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Anti-Inflammatory and Analgesic Profile of Amidines of 3-Amino-1,2,4-benzotriazine and 3-Amino-1,2,4-benzotriazine-1-oxide

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Abstract □ Several formamidine and acetamidine derivatives prepared from 3-amino-1,2,4-benzotriazine and 3-amino-1,2,4-benzotriazine-1-oxide displayed an aspirin-like anti-inflammatory and analgesic profile. The test systems included adjuvant-induced arthritis in rats, carrageenan-induced edema in rats, UV-induced erythema in guinea pigs, the analgesic gait test, the antipyretic test, and GI ulcer studies.

Keyphrases □ Anti-inflammatory activity—amidine derivatives of 3-amino-1,2,4-benzotriazines and their 1-oxides, synthesis and testing, rats □ Analgesic activity—amidine derivatives of 3-amino-1,2,4-benzotriazines and their 1-oxides, synthesis and testing, rats □ 3-Amino-1,2,4-benzotriazines—amidine derivatives, synthesis and testing for anti-inflammatory and analgesic activity, rats

Various new, nonsteroidal, anti-inflammatory agents such as ibuprofen, tolmetin, fenoprofen, naproxen, and sulindac have been introduced to the medical community in the past several years (1). Although these agents ameliorate the arthritic condition, they are not curative and have adverse effects, largely GI disturbances (1).

The continuing interest and need for more efficacious and safe anti-inflammatory agents prompted the synthesis of various formamidine and acetamidine derivatives of 3-amino-1,2,4-benzotriazine and 3-amino-1,2,4-benzotriazine-1-oxide. These agents were tested for analgesic, anti-inflammatory, and antipyretic properties in a battery of tests including adjuvant-induced arthritis, carrageenan-induced edema, and UV-induced guinea pig erythema (2, 3). Particular emphasis was placed on GI toxicity. The results are presented, and the potential of the active series is discussed.

RESULTS AND DISCUSSION

Chemistry—The amidines were prepared by the reaction of the

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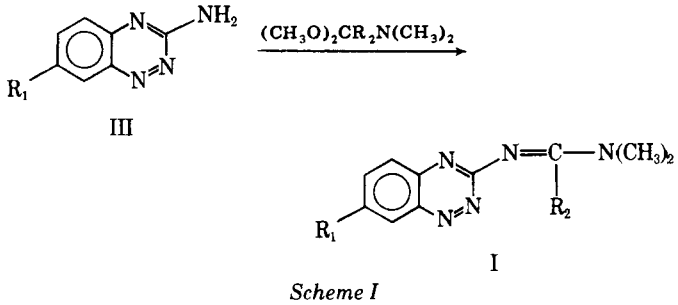
Table I—Amidine Derivatives Prepared from 3-Amino-1,2,4-benzotriazines and Their 1-Oxides

Compound	R_1	R_2	Melting Point	Yield, %	Molecular Formula	Analysis, %	Calc.	Found
Ia	F	H	106–109°	48	$C_{10}H_{10}FN_5$	C	54.78	54.62
						H	4.60	4.56
						F	8.67	8.77
						N	31.95	32.03
Ib	CH_3	H	98–101°	75	$C_{11}H_{13}N_5$	C	61.37	61.28
						H	6.09	6.18
						N	32.24	32.03
Ic	H	H	100–103°	65	$C_{10}H_{11}N_5$	C	59.68	59.53
						H	5.51	5.45
						N	34.81	34.77
Id	Cl	H	135–137°	84	$C_{10}H_{10}ClN_5$	C	50.96	50.93
						H	4.28	4.36
						Cl	16.05	15.91
						N	29.72	29.95
Ie	F	CH_3	125–126.5°	31	$C_{11}H_{12}FN_5$	C	56.74	56.65
						H	5.37	5.19
						F	8.06	8.15
						N	30.21	30.03
If	Cl	CH_3	141.5–143°	68	$C_{11}H_{12}ClN_5$	C	52.91	52.98
						H	4.84	4.69
						Cl	14.20	13.89
						N	28.05	28.11
IIa	F	H	188–190°	72	$C_{10}H_{10}FN_5O$	C	51.06	51.07
						H	2.48	4.12
						F	8.08	8.28
						N	29.78	30.03
IIb	CH_3	H	148–150°	61	$C_{11}H_{13}N_5O$	C	57.10	56.96
						H	5.66	5.83
						N	30.29	30.36
IIc	H	H	156–158°	58	$C_{10}H_{11}N_5O$	C	55.29	55.28
						H	5.10	5.22
						N	32.24	32.35
IId	Cl	H	177–178°	64	$C_{10}H_{10}ClN_5O$	C	47.72	47.95
						H	4.00	3.95
						Cl	14.09	14.06
						N	27.83	27.75
IIe	Br	H	162–164°	35	$C_{16}H_{10}BrN_5O$	C	40.56	40.24
						H	3.40	3.23
						Br	26.99	26.90
						N	23.65	23.90
IIf	F	CH_3	158–160°	19	$C_{11}H_{12}FN_5O$	C	52.77	53.01
						H	4.86	4.86
						F	7.48	7.62
						N	28.22	28.11



Scheme I

aminobenzotriazines (III) and their 1-oxides (IV) with excess dimethylformamide dimethylacetal or dimethylacetamide dimethylacetal (Schemes I and II).

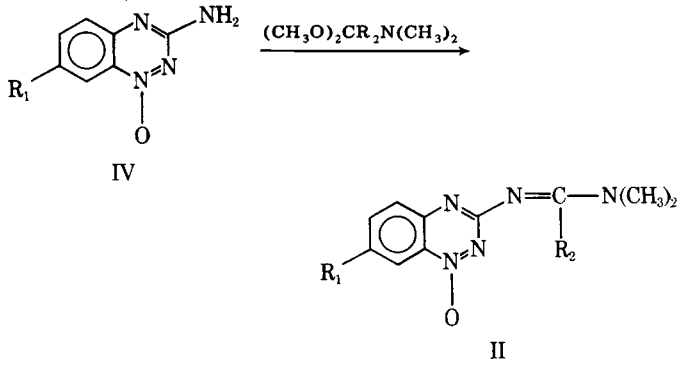
Workup gave the derivatives of III (I) and the derivatives of IV (II) in 20–85% yields. Table I lists the 12 synthesized amidines.

Biological—Amidines Ia–If and IIa–IIf were first evaluated for activity against adjuvant-induced arthritis in rats (4). Groups of three Royal Hart Wistar rats, 200 ± 10 g, were injected intradermally in the right hindpaw with dried human tubercle bacilli in a mineral oil vehicle[1] at 2 mg/kg. The test compounds were administered orally in a 1.5% starch vehicle at the indicated dosage (Table II) once daily on Days 0–13 postchallenge. Control rats were treated similarly but were given the starch vehicle instead of the test compound.

On Days 14 and 21 postchallenge, the diameter of the injected paw (primary lesion) was measured with a micrometer caliper (6), the volumes of the inflamed paws were estimated from these measurements, and the results were expressed as percent inhibition of swelling as compared to 12 controls. If the percent inhibition was ≥24%, the compound was tested again. After the second test, the mean inhibition of swelling for both tests was calculated; if it was ≥26%, the compound was tested a third time. If the mean inhibition of all three tests was ≥25%, the compound was accepted as active. Such compounds were completely retested again in the same manner to confirm activity. Thus, no compound was considered to have confirmed activity until the test was repeated a minimum of six times (total of 18 rats).

In the dose–response experiments, the other inflamed sites such as the ears, paws, and tail (secondary lesions) were observed and graded. The mean grade was calculated and similarly expressed as the percent inhibition as compared to controls.

The active compounds (those showing at least 25% mean inhibition



Scheme II

[1] Freund's adjuvant.

Table II—Pooled Data [a] for Adjuvant-Induced Arthritis

Compound	Oral Dose[b], mg/kg	Dead/Treated at 21 Days	Percent Inhibition of Swelling (Primary Lesion) Day 14	Percent Inhibition of Swelling (Primary Lesion) Day 21	Percent Inhibition of Control Grade (Secondary Lesion) Day 14	Percent Inhibition of Control Grade (Secondary Lesion) Day 21
Indomethacin[c]	2	8/57	51[d]	24[d]	38[d]	25[d]
	1	9/54	46[d]	19[d]	34[d]	20[d]
	0.5	5/54	40[d]	20[d]	25[d]	17[d]
	0.25	0/9	30[d]	4[d]	22[d]	4[d]
Aspirin[c]	400	18/57	73[d]	48[d]	58[d]	45[d]
	200	10/66	48[d]	27[d]	26[d]	17[d]
	100	18/63	36[d]	13	19[d]	8
	50	2/21	23[d]	3	12	9
I*a*	100	6/18	54[d]	44[d]	73[d]	48[d]
	50	6/33	51[d]	26[d]	69[d]	49[d]
	25	2/18	49[d]	24[d]	31[d]	0
I*d*	100	1/18	66[d]	24	83[d]	54[d]
	50	2/36	46[d]	15	36[d]	20[d]
	25	1/18	41	16	30[d]	18
II*a*	100	12/18	77[d]	76[d]	97[d]	82[d]
	50	5/36	51[d]	31[d]	65[d]	40[d]
	25	3/18	29[d]	19	35[d]	24[d]
I*b*	50	5/36	0	0	—	—
I*c*	50	0/3	27	5	—	—
I*e*	50	3/6	17	0	—	—
I*f*	50	2/18	59[d]	29[d]	—	—
II*b*	50	0/3	0	0	—	—
II*c*	50	0/3	0	0	—	—
II*d*	50	1/18	46[d]	13	—	—
II*e*	50	1/3	24	0	—	—
II*f*	50	0/3	12	32	—	—

[a] There were 12 control arthritic rats in each experiment with six treated rats per group in dose–response experiments and three treated rats per group in screening tests. Each experiment was repeated several times, as reflected by the total number of animals shown. Statistical comparisons were performed using paw diameters or arthritic grades, although results were expressed as percent inhibition. The statistical significance of each test result also was determined by a *t* test. Since the data from all available testing were pooled, the probabilities obtained in the individual Student *t* test analysis were combined as described by Snedecor and Cochran (5). For the control rats, eight of 186 had died by Day 21. [b] By gavage. [c] Historical data. [d] Statistically significant activity ($p < 0.05$) by the Student *t* test).

of swelling based on a total of 18 rats) then were tested against acute inflammatory conditions in carrageenan-induced edema in rats and UV-induced erythema in guinea pigs.

The method for the carrageenan-induced edema assay used was similar to that described by Winter *et al.* (7). Royal Hart Wistar rats, 80–90 g, were fasted overnight prior to dosing but had free access to water. Drugs in an aqueous suspension were administered by gavage in a volume of 1.7 ml/50 g of body weight (corresponding to the hydration volume used by Winter *et al.*).

The phlogistic agent, carrageenan[2], was prepared as a sterile 1% suspension in 0.9% NaCl for routine testing. A volume of 0.05 ml was injected through a 26-gauge needle into the plantar tissue of the right hindpaw. Measurements were made 5 hr after drug administration (4 hr after carrageenan challenge) unless otherwise indicated.

Volumes of both the normal and carrageenan-inflamed feet were determined, and the difference between the two measurements was considered to be the increased edema due to carrageenan administration. Results were expressed as a C/T efficacy ratio (mean edema of control animals/mean edema of treated animals). Each screening test had eight control rats and two treated rats. If the C/T ratio was ≥1.41, the test was repeated. If the mean ratio for Tests 1 and 2 was >1.43, the compound was considered active and the procedure was repeated for confirmation. Thus, no compound was considered to have confirmed activity until each test was repeated four times (32 controls, eight treated rats). The results for the amidines along with several reference agents are listed in Table III.

The method used to determine erythema in guinea pigs was similar to that of Winder *et al.* (8). Albino guinea pigs[3] were depilitated on their flanks the evening before testing with a standard mixture of barium sulfide and gum acacia. On the morning of testing, groups of four guinea pigs were dosed by gavage 1 hr prior to UV exposure (−1 hr). At 0 hr, they were restrained in a plastic container, which allowed exposure of three circular spots. They then were exposed to UV irradiation[4] for 60 sec. At +1 and +4 hr, the degree of erythema for each of the three sites was assessed according to the following scoring system: 0 = no erythema, 0.5 = incomplete circle or faint erythema, and 1.0 = complete circle of distinct erythema. Thus, the maximum score for each animal was 3.0. The results for a select group of amidines and reference drugs are shown in Table IV.

A modification of the method described by Atkinson and Cowan (9) was used to assess analgesic activity. A 40% suspension of Brewer's yeast in normal saline (0.25 ml/rat) was injected into the plantar surface of the left hindpaw of each rat. After 3 hr, predrug assessment of walking gait on a wire-mesh platform was made for each rat according to the following scoring system: 0 = normal gait, 0.5 = intermittent mild limp, 1 = constant limp with continuous use of foot pad, 1.5 = limping with occasional three-legged gait or intermittent use of digits in combination with foot pad, and 2 = continuous three-legged gait or continuous use of only the tips of the digits without any use of the inflamed foot pad.

Rats with a score of <2 were excluded from the experiment. The test compounds or vehicle then were administered orally to groups of six rats, and postdrug assessments were recorded after 90 min. A positive analgesic response was considered to be a ≥50% reversal of the pretreatment score (*i.e.*, posttreatment score of ≤1).

For selected compounds, subsequent experiments were performed with at least three graded dosage levels and five rats per group. Pre- and postdrug assessments were made as described.

The dose estimated to cause a positive analgesic response in 50% of the rats (ED_{50}) was calculated according to the arc-sine linear transformation method of Finney (10). The ED_{50} values for the remaining compounds were approximated.

The effect of the amidines on experimental elevated temperatures was examined during the analgesic gait test. The body temperature of rats increases after the plantar injection of Brewers' yeast, thus providing a good experimental model for studying antipyresis.

The rectal temperature of each rat was measured immediately after pretreatment scoring of abnormal gait by a rectal probe[5]. Ninety minutes after treatment with the compounds, the temperature was recorded again. The average change of each group of rats was calculated from the difference of the pretreatment and posttreatment temperatures.

The antipyretic and analgesic data are summarized in Table V.

GI ulcer studies were conducted in male Royal Hart Wistar rats weighing 190–210 g. The rats were distributed among control and treatment groups (five rats per group) and housed with one rat per cage. During the 52-hr test period, the rats were permitted free access to food and drinking water for the first 33 hr but were fasted overnight prior to

[2] Viscarin, obtained from Marine Colloids.
[3] Lederle breeding colony.
[4] Model 10 "Hanovia" Kromayer lamp.
[5] Yellow Springs telethermometer.

Table III—Pooled Data [a] of Carrageenan-Induced Edema of Rat Paws

Compound	Oral Dose, mg/kg	Number of Rats	C/T[b]
Controls		64	1.0
Aspirin[c]	250	32	2.8[d]
	83	32	1.4[d]
Phenylbutazone[c]	250	32	2.3[d]
	83	32	2.4[d]
	27	32	1.7[d]
Indomethacin[c]	250	32	2.9[d]
	83	32	2.3[d]
	27	32	2.2[d]
	9	32	2.0[d]
	3	32	1.5[d]
Ia	250	12	3.1[d]
	83	12	3.0[d]
	27	12	1.6[d]
Id	250	12	2.5[d]
	83	12	2.1[d]
IIa	250	12	3.4[d]
	83	12	2.8[d]
	27	12	1.6[d]
Ib	250	2	1.0
Ic	250	8	3.6[d]
Ie	250	2	2.4[d]
If	125	8	3.4[d]
IIc	250	8	2.7[d]
IId	250	8	2.6[d]
IIf	60	2	1.2

[a] There were eight control edematous rats in each experiment with four rats per treated group in dose–response experiments and three rats per treated group in screening tests. Each experiment was repeated several times, as reflected by the total number of rats shown. Statistical comparisons were performed using rat paw edema volumes, although the results were expressed as control/treated ratios. The statistical significance of each test result was determined by the Student *t* test. Since all available data were pooled, the probabilities obtained in each individual Student *t* test were combined as described by Snedecor and Cochran (5). [b] Edema of control animals/edema of treated animals. [c] Historical data. [d] Active ($p < 0.05$ by the Student *t* test).

Table IV—Effects on UV-Induced Erythema in Guinea Pigs [a]

Compound	Average Score 1 hr	Average Score 4 hr	Number of Guinea Pigs
Control[b]	2.1	2.8	364
Aspirin[b]	0.1[c]	2.0	16
Phenylbutazone[b]	0.1[c]	1.1[c]	16
Indomethacin[b]	0.1[c]	1.3[c]	12
Ia	0.2[c]	1.6	8
Ib	1.0[c]	2.3	4
If	0.4[c]	2.6	8
IIa	0.2[c]	1.7	8
IId	0.9[c]	2.2	8

[a] The dose was 125 mg/kg po. [b] Historical data. [c] Active ($p < 0.05$ by the Student *t* test).

Table V—Analgesic and Antipyretic Activity

Compound	Reversal of Abnormal Gait, ED_{50}, mg/kg po (95% confidence limit)	Inhibition of Yeast-Induced Pyresis Temperature Change, °F (dose, mg/kg po)
Ia	20 (4–91)	−2.7 (100)
Ic	~100	−4.1 (200)
Id	79 (52–120)	−1.5 (100)
IIb	~200	+0.9 (200)[a]
IIc	107 (58–202)	−1.5 (200)
IIe	~150	−0.1 (200)[a]
IIa	35 (10–120)	−3.0 (100)
Aspirin	93 (53–163)	−1.3 (200)
Vehicle	—[b]	+0.2[a]

[a] Inactive. [b] No reversal of abnormal gait.

sacrifice. Drugs were suspended in a 1.5% starch–phosphate buffer solution and injected by gavage or subcutaneously twice daily on Days 0 and 1. The rats received only one injection on Day 2, and 6 hr later they were killed with chloroform.

The stomachs were dissected, opened along the greater curvature, and rinsed briefly in tap water. They then were spread with the mucosal surface facing upward and were pinned onto corks (6.35-cm diameter) individually numbered on the back. The identification number for each stomach was not known to the investigator, and the stomachs were randomly graded according to the following scheme (11): 0 = normal; 1 = petechial hemorrhage or pinpoint ulcers; 2 = one or two small ulcers or hemorrhagic erosions; 3 = many areas of hemorrhagic erosion or ulcers, a few large; and 4 = massive areas of hemorrhagic erosion or many ulcers, mainly large.

The intestines also were removed and examined for ulcers. The intensity of intestinal ulceration was graded according to the following scheme: 0 = normal intestine; 1 = mucosa thin, petechial hemorrhage; 2 = "blow-outs" (intestine inflated with air); 3 = few ulcers—gut more fragile than normal and tears along line of mesentery attachments when removed; and 4 = many large perforating lesions, adhesions, gut hemorrhage (very fragile and tears readily and cannot be removed intact; *graded in situ*).

The results of two amidines and reference drugs are shown in Table VI.

Of the amidines reported in Table I, Ia, Id, IIa, and IId had the broadest scope of anti-inflammatory and analgesic activity, showing that the 3-amino-1,2,4-benzotriazines and 3-amino-1,2,4-benzotriazine-1-oxides with a fluorine or chlorine in the 7-position were the most active. The difference between the activity of the parent and the *N*-oxide in pairs Ia and IIa and Id and IId was marginal. Of the nonhalogenated compounds, Ib, featuring a methyl group at C-7, possessed significant activity in most tests.

The acetamidines Ie, If, and IIf were active, but If and IIf were significantly lower in overall activity than their formamidine counterparts. 7-Fluoroacetamidine (Ie) was slightly less active than Ia overall.

Many of the amidines tested in the anti-inflammatory and analgesic tests possessed an acceptable therapeutic index. However, one serious side effect involves ulceration or hemorrhaging in the GI tract. Two of the most interesting compounds, Ia and IId, were administered to rats, and the GI tracts were examined (Table VI). Both compounds exhibited severe GI problems in the form of gastric ulceration and hemorrhaging. At doses of 200 and 100 mg/kg, respectively, both exhibited a gastric ulcer grade of 3.6–4.0 out of a possible 4.0. The severe GI ulceration and hemorrhaging problem precludes further development of amidines of 3-amino-1,2,4-benzotriazines and their 1-oxides.

EXPERIMENTAL[6]

Preparation of Amidines (12, 13)—A suspension of the aminobenzotriazine or *N*-oxide in dimethylformamide dimethylacetal or dimethylacetamide dimethylacetal was stirred and heated under reflux for 5 hr. If solution was not attained, 10–20 ml of dimethylformamide or dimethylacetamide was added at the 2-hr point. The excess acetal was removed *in vacuo*, and the residue was recrystallized directly or chromatographed and recrystallized.

***N'*-(7-Fluoro-1,2,4-benzotriazin-3-yl)-*N,N*-dimethylformamidine (Ia)**—A suspension of 10 g (0.06 mole) of 3-amino-7-fluoro-1,2,4-benzotriazine in 20 ml of dimethylformamide dimethylacetal was refluxed for 5 hr. On cooling, the solution was evaporated to dryness *in vacuo*. The residue was recrystallized twice from chloroform–hexane, giving yellow-orange plates, mp 106–109° (6.3 g, 48% yield); NMR ($CDCl_3$): 3.15 (s, 3), 3.20 (s, 3), 7.5 (m, 1), 7.7 (m, 1), 7.95 (m, 1), and 8.95 (s, 1).

***N'*-(7-Chloro-1,2,4-benzotriazin-3-yl)-*N,N*-dimethylformamidine (IId)**—A suspension of 10 g of 3-amino-7-chloro-1,2,4-benzotriazine in 20 ml of dimethylformamide dimethylacetal was refluxed for 5 hr. On cooling, the solution was evaporated *in vacuo*. The residue was recrystallized from chloroform–hexane, giving 10.1 g (84% yield) of orange needles, mp 135–137°; NMR ($CDCl_3$): 3.3 and 3.5 (s, 6), 7.6 (aryl, 2), 8.21 (aryl, 1), and 8.88 (s, 1).

[6] All melting points were taken on a Mel-Temp apparatus. Samples for elemental analyses were dried at 55° for 5–24 hr. NMR spectra were determined with a Varian model HA-100 spectrometer; chemical shifts are reported in parts per million relative to the internal standard tetramethylsilane.

Table VI—GI Ulcer Studies

Compound	Oral Dose[a], mg/kg	Dead/Treated	Grade of Gastric Ulcer[b] (95% confidence limits)	Grade of Intestinal Ulcer (95% confidence limits)
Aspirin[c]	250	0/9	2.7 (1.8–3.6)	0.6 (0–1.5)
	83	0/10	1.7 (0.9–2.5)	0
	27	0/10	1.1 (0.5–1.7)	0
Indomethacin[c]	27	2/10	2.0 (1.6–2.4)	3.5[d] (3.1–3.9)
	9	0/10	2.2 (1.0–3.4)	3.4[d] (2.6–4.0)
	3	5/10	1.1 (0.4–1.8)	1.1 (0.4–1.8)
Phenylbutazone[c]	150	2/10	2.0 (1.4–2.6)	0.6 (0–1.2)
	50	0/10	0.3 (0–0.8)	0
	12	0/10	0.5 (0–1.1)	0
Ia	200	4/5	3.6[d] (2.8–4.0)	1.0 (0–2.4)
	100	0/5	3.8[d] (3.2–4.4)	0
Id	200	0/5	4.0[d] (3.2–4.5)	0
	100	0/5	3.6[d] (2.8–4.0)	0
Controls	—	0/25	0.2 (0–0.4)	0

[a] Twice daily for 2 days and once on the 3rd day for a total of five doses. [b] Both the stomach and the intestines were removed during the autopsy and inspected for lesions. The severity of lesions was expressed by a grading system ranging from 4 (many large ulcers or severe hemorrhagic erosion) to 0 (normal). [c] Historical data. [d] Severe GI hemorrhaging.

***N'*-(7-Bromo -1,2,4- benzotriazin-3-yl-1-oxide) -*N,N*- dimethylformamidine (IIe)**—A suspension of 10 g of 3-amino-7-bromo-1,2,4-benzotriazine-1-oxide was refluxed in 20 ml of dimethylformamide dimethylacetal. At 2 hr, a suspension still was evident; 10 ml of dimethylformamide was added, and reflux was resumed for 3 hr more. After cooling, the excess acetal was removed *in vacuo*. The residue was dissolved in chloroform, filtered through a silica gel plug, and heated to reflux. Hexane was added to induce cloudiness, and the solution was cooled, giving 5.1 g (35% yield) of yellow-brown cubes, mp 162–164°; NMR ($CDCl_3$): 3.26 and 3.29 (s, 6), 7.7 (d, 1, J = 8 Hz), 7.7 (d of d, 1, J = 1.0 and 8.1 Hz), 8.5 (d, 1, J = 1 Hz), and 8.8 (s, 1).

***N'*-(7-Fluoro - 1,2,4 - benzotriazin - 3-yl-1-oxide)-*N,N*-dimethylacetamidine (IIf)**—A solution of 10 g (0.056 mole) of 3-amino-7-fluoro-1,2,4-benzotriazine-1-oxide in 22 ml of dimethylacetamide dimethylacetal was refluxed for 5 hr and cooled, and the excess acetal was evaporated to dryness under vacuum. The residue was eluted through a short silica gel column with 20% ethyl acetate in hexane to provide 2.6 g (19% yield) of II*f*, mp 158–160°; NMR ($CDCl_3$): 2.24 (s, 3), 3.18 (s, 6), and 7.3–8 (m, 3).

***N'*-(7-Chloro-1,2,4-benzotriazin-3-yl) -*N,N*- dimethylacetamidine If)**—A solution of 5.0 g (0.03 mole) of 3-amino-7-chloro-1,2,4-benzotriazine in 11 ml of dimethylacetamide dimethylacetal was refluxed for 4 hr. The solution then was cooled, and the excess acetal was removed under vacuum. The residue was recrystallized from chloroform–hexane to yield 4.7 g of I*f* (58% yield), mp 141.5–143°; NMR ($CDCl_3$): 2.28 (s, 3), 3.26 (s, 6), 7.72 (m, 2), and 8.30 (m, 1).

***N'*-(7-Fluoro-1,2,4-benzotriazin-3-yl) -*N,N*- dimethylacetamidine (Ie)**—A solution of 10 g (0.06 mole) of 3-amino-7-fluoro-1,2,4-benzotriazine in 20 ml of dimethylacetamide dimethylacetal was refluxed for 5 hr. On cooling, the solution was evaporated to dryness under vacuum. The residue was dissolved in chloroform, eluted through a pad of silica gel, and concentrated. Trituration of the concentrate with petroleum ether (bp 30–60°) produced 9.4 g of a crystalline product (31% yield), mp 125–126.5°; NMR ($CDCl_3$): 2.24 (s, 3), 3.24 (s, 6), and 7.4–8.1 (m, 3).

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