Pharmacokinetics of Aryldihydro-*s*-triazines with Antifolate Activity II: Blood Levels and Their Relevance to Antineoplastic Activity in Rats

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Abstract □ Blood levels of three aryldihydro-*s*-triazines in rats were followed: 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-phenyl-*s*-triazine (I), the prototype of the series; 4,6-diamino-1-(3,4-dichlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (II); and *N*-(*m*-tolyl)-*p*-(4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazin-1-yl)hydrocinnamide (III). The blood profiles obtained provide substantial evidence that III, but not II, was precipitated in the peritoneal cavity where it was injected. Precipitation after intraperitoneal injection may explain why III and similar triazines with long nonpolar chains have been reported to be more active against intraperitoneal Walker 256 tumor than is II, even though the latter compound is a far more potent inhibitor of Walker 256 dihydrofolate reductase and of tumor cell cultures *in vitro*. Precipitation in the peritoneal cavity also may be involved in the difficulty of obtaining the toxicity-free antineoplastic activity expected from certain aryldihydrotriazines selectively inhibiting neoplastic dihydrofolate reductase.

Keyphrases □ Triazines, various substituted—blood levels related to antineoplastic activity, rats □ Blood levels—various substituted triazines, related to antineoplastic activity, rats □ Antineoplastic activity—various substituted triazines, related to blood levels, rats

To produce cancer chemotherapeutic agents with less toxicity than that accompanying the clinical use of methotrexate, antifolate compounds selectively inhibiting dihydrofolate reductase from neoplastic tissues have been sought (1, 2). However, while many of these compounds exhibit impressive ability to prolong survival of animals bearing tumors, their isoenzyme selectivity has not given rise to a demonstrable protection from toxicity. Furthermore, no certain relationship between the antifolate and the antineoplastic potencies of these and related compounds has been found.

In a previous study (3), the metabolism and excretion of two test compounds provided no positive explanation for the reversal in their relative antifolate and relative antineoplastic potencies. In another approach to understanding this anomaly, a study of the blood levels of these aryldihydro-*s*-triazines is now described.

EXPERIMENTAL

Synthetic Methods—The triazines studied were: 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-phenyl-*s*-triazine (I), 4,6-diamino-1-(3,4-dichlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (II), and *N*-(*m*-tolyl)-*p*-(4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazin-1-yl)hydrocinnamide (III). Their syntheses were described previously (3).

Radiotracer Techniques—Radioisotope levels were measured with a liquid scintillation spectrometer[1]. Bray's scintillation solution was used for counting the activity of injections (4). Whole blood (0.2 ml) was mixed thoroughly with 1.5 ml of a digestant solution[2] in a preweighed scintillation vial. Aqueous hydrogen peroxide solution (0.5 ml, 27.5% w/w) was then incorporated. After at least 30 min, a scintillation solution[3] (15 ml) was added; the vial was shaken well and stored in the counter for at least 2 hr before counting.

Animal Techniques—Male Wistar rats[4], 250–300 g and 3–6 months old, were used after maintenance for 1–4 months in an environment untreated with insecticides. They received a commercial diet formulated for laboratory mice and rats. Blood was sampled no sooner than 12 hr after implantation of a jugular cannula (5). No animal was used for experimentation more than once.

RESULTS

A 5-mg ip dose[5] of I, II, or III was given to each of eight animals. Representative blood level curves are shown in Fig. 1. The concentrations of all three compounds in blood were low, indicating high volumes of distribution. At its peak, the blood I concentration was only 0.17% of the dose/g of blood. [A 250-g rat has about 20 g of blood (6).] Concentrations of II in the blood were even lower, while III reached radioactivity levels in the blood only about one-seventh those attained by I.

Following peaks close to 15 min after dosing, blood concentrations of both I and II declined rapidly. The blood levels from a dose of III showed a broad peak, which yielded to a (log) rate of decline similar to those of the other triazines after about 1 hr. The comparative long-term persistence of II in blood predicted from urinary excretion rate plots (3) was confirmed.

All blood level curves presented show the radioactivity in blood resulting from a dose of labeled triazine. Previous data (3) indicated that I and II were not metabolized; therefore, radioactivity levels in blood reflect the concentrations of these administered species. (The persistent tail of the blood profile for II might reflect some very minor, enduring metabolite.) Compound III, in contrast, was significantly metabolized. Blood radioactivity, therefore, gives no direct information on unchanged III.

Additional uncertainty arises in that metabolites may be distributed differently from their parent compounds (7). If the volumes of distribution are appreciably different, irregularities in blood curves based on total radioactivity in the sampled volume may occur. These irregularities could be especially noticeable if emerging metabolites have considerably lower volumes of distribution than their parent and, thus, the influence of metabolism on the total concentration (radioactivity) is counter to that of excretion.

Unusual Absorption Peak for III—Compared to the absorption peaks obtained with I and II, the peak due to III was low and of an unusual and broad shape. The lower radioactivity in blood than that succeeding a dose of either I or II may have been due to a considerably greater volume of distribution of III. In such a situation, the production of metabolites with lower volumes of distribution than that of III may have led to peaks subsequent to the absorption peak, which, if sufficiently close, may have been misinterpreted as an extension of the absorption peak.

More frequent monitoring of blood early after a 5-mg ip injection of III showed that consistent decay of blood levels might not commence until about 2 hr after dosing. If, however, the extended plateau observed was in some way due to peaks in total blood radioactivity caused by the production of metabolites, these peaks were not in evidence following a 1-mg iv (jugular) dose[6] to three rats (Fig. 2). Given the minor chemical differences between III and its two metabolites (3), close similarity in their biological distributions should not be surprising.

Slow first-order absorption of III may have been expected to lead to slow attainment of a peak blood level and then decay, *i.e.*, a broad but definite peak. Characteristically, however, in the first sample after intraperitoneal dosage, the 5-min sample, maximum blood levels or a little

[1] Tri-Carb model 3314, with automatic external standardization, model 3950, Packard Instrument Co.
[2] A 1:1 mixture of 2-propanol and Soluene 100 (Packard).
[3] A 1:9 mixture of 0.5 *N* HCl and Insta-gel (Packard).
[4] University of Sydney Animal House, Castle Hill, New South Wales.
[5] Unless otherwise specified, all triazines were injected in a 10-mg/ml solution in 60% dimethyl sulfoxide in water.
[6] The lethal dose of any of the triazines by the intravenous route was little more than 1 mg.

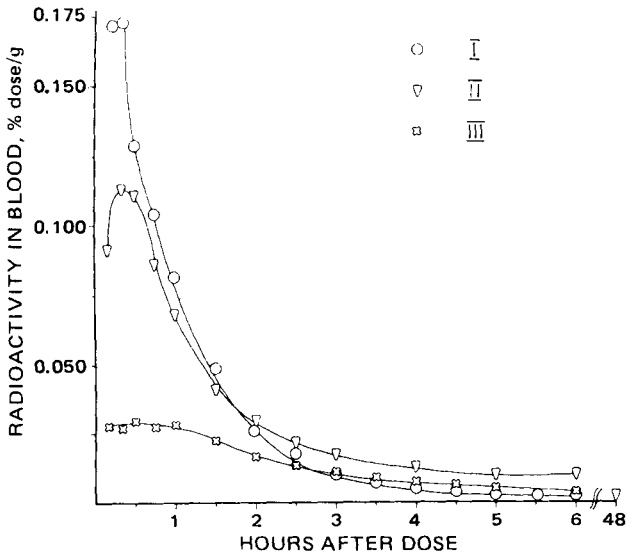

Figure 1—*Representative blood level curves after 5 mg ip of I, II, or III.*

less had already been achieved. A slight drop in level in the 10-min sample and a subsequent return toward the level of the 5-min sample were followed by relatively steady levels. A consistent decline in blood levels commenced only about 60–120 min after dosage.

The profile to this point, a plateau rather than a peak, was similar to that obtained when steady-state blood levels are generated by an intravenous bolus dose followed by a constant intravenous infusion (8–10). An approximately analogous situation might have been expected if the administered compound, injected in a nonaqueous solvent, had precipitated in the peritoneal cavity because of dilution of the solvent with peritoneal fluid or because of more rapid absorption of the solvent than the dosed compound (11). Precipitation by either or a combination of these mechanisms may have abruptly terminated the initial rapid rate of first-order absorption following intraperitoneal injection.

A later phase of constant low level absorption may have been driven by the low concentration in the aqueous peritoneal fluid, constant at saturation level unless further limited by the redissolution rate of the precipitate. Following complete redissolution, however, a consistent decline in the content of the peritoneal fluid, the absorption rate, and the blood level could have been expected.

Testing Precipitation Model—The III injection solution (0.5 ml, 10 mg/ml in 60% dimethyl sulfoxide) was diluted with 1 ml of water. Within 2 hr, some opalescence was apparent; after overnight standing, large crystals (still growing) were observed. The supernate, probably still a colloidal suspension, held about one-third of the radioactivity. In contrast, I and II were soluble at 10 mg/ml of pure water. Not surprisingly, precipitate was not visible upon opening the peritoneal cavity shortly after injecting III.

Varying Volume of Injection Solvent—If the initial peak in blood levels of III was due to an initial rapid first-order absorption terminated by the precipitation of this compound upon dilution or absorption of the injection solvent, an increase in the solvent volume injected should increase the duration and height of the initial peak. Furthermore, this increase should curtail the subsequent plateau since, with increased early absorption, less compound should precipitate, thereby shortening the time required for its complete redissolution. In the limiting situation, it can be envisaged that the initial peak should not be delayed or augmented further by increased solvent injection since all of the compound would be absorbed before it could precipitate and no trailing plateau would be observed; *i.e.*, the conventional profile should result.

Fifteen animals were dosed with 5 mg ip of III in 0.5, 1.0, or 2.0 ml of 60% dimethyl sulfoxide (Fig. 3). The predicted increase in height and width of the initial peak was seen after increasing the solvent volume from 0.5 to 1.0 ml (height changed from 0.029 to 0.050% of the dose/g of blood; $p < 0.05$ by two-tailed t test). Dosing in 2.0 ml of solvent also produced a greater peak than dosing in 0.5 ml (0.047% of the dose/g of blood; $p < 0.05$), but, in agreement with the prediction of a limit to the increase, the peak after dosing in 2.0 ml was no greater than that after dosing in 1.0 ml of solvent.

The blood profiles obtained with the larger dose volumes, however, were not always ideal; periods of stationary blood levels or after-peaks

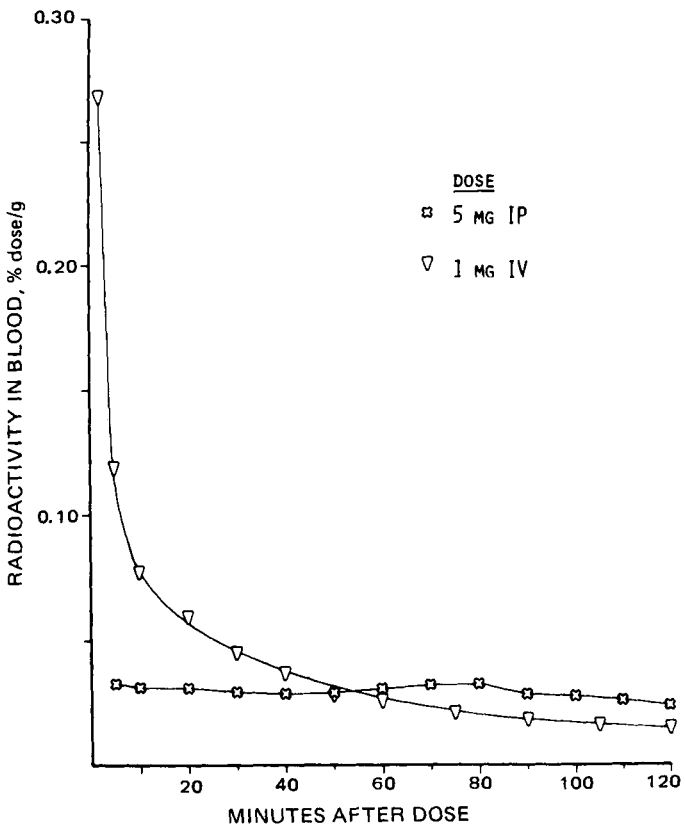

Figure 2—*Representative blood level curves after 1 mg iv or 5 mg ip of III.*

were particularly noticeable in profiles exhibiting smaller initial peaks, as would be expected if the compound was still precipitating in these cases.

A dose of 2.5 mg ip of III in 0.25, 0.5, or 1.0 ml of 60% dimethyl sulfoxide was given to 15 animals (Fig. 4). All profiles except one showed plateaus or large secondary peaks. No significant difference was found by a t test between the heights of initial peaks after 2.5-mg doses in the three injection volumes. This result, however, could have been due to the considerable variability observed. Variability, which is not a surprising

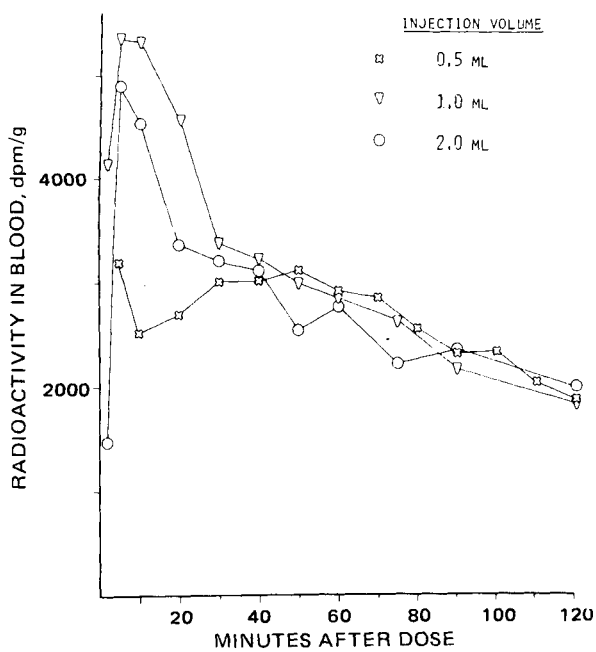

Figure 3—*Representative blood level curves after 5 mg ip of III in 0.5, 1.0, or 2.0 ml of 60% dimethyl sulfoxide.*

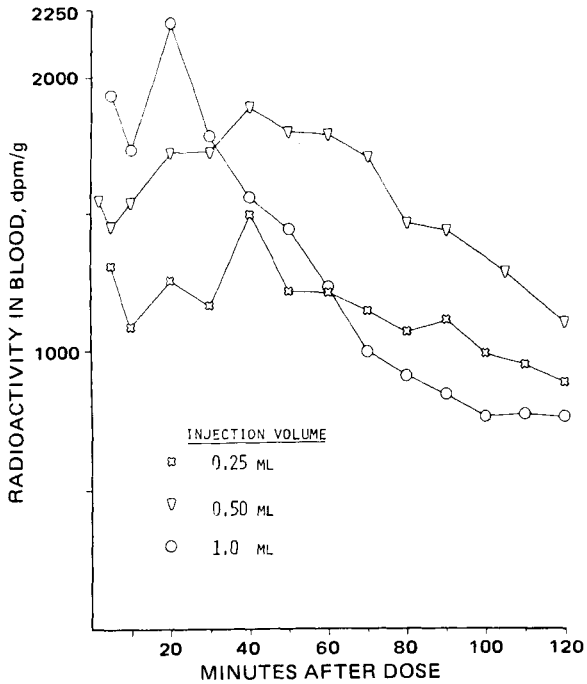

Figure 4—*Representative blood level curves after 2.5 mg ip of III in 0.25, 0.5, or 1.0 ml of 60% dimethyl sulfoxide.*

consequence of the complexity of factors that might impinge on precipitation in the peritoneal cavity, appears to have diminished with an increase in dose volume. The average height of initial peaks was 0.029 ± 0.007 (*SE*), 0.028 ± 0.004, or 0.039 ± 0.003% of the 2.5-mg dose/g of blood after dosing in 0.25, 0.5, or 1.0 ml (five rats per injection volume).

Varying Dose—Doses of 2.5, 5, or 10 mg ip of III were given in the same injection volume of 1.0 ml of 60% dimethyl sulfoxide. In Fig. 5, profiles with few irregularities have been chosen as examples for 2.5- and 5-mg dosing. All five animals dosed with 10 mg in 1.0 ml had irregular blood profiles. The comparatively smooth curves resulting from the lower two doses in 1.0 ml had an interrelationship approximately that expected if no precipitation had occurred. The irregular profile representing the 10-mg dose, however, had an initial peak of similar magnitude to that

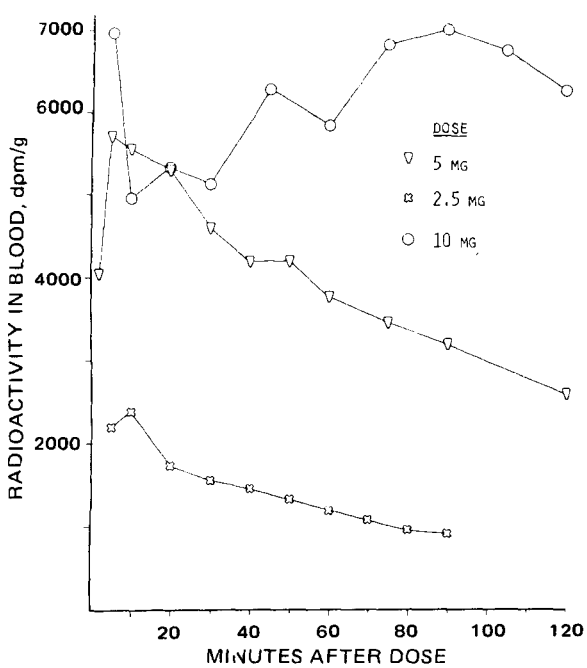

Figure 5—*Representative blood level curves after intraperitoneal dose of 1.0 ml of 60% dimethyl sulfoxide containing 2.5, 5.0, or 10 mg of III.*

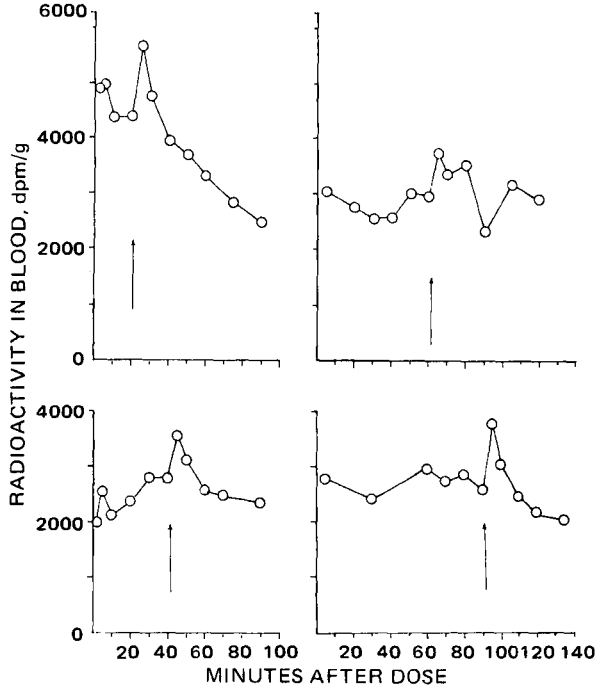

Figure 6—*Representative blood level curves showing the effect of a 60% dimethyl sulfoxide chase injection approximately 20, 40, 60, or 90 min after 5 mg ip of III.*

following a dose of only 5 mg in the same volume of solvent. In the very early period after either dose, similar amounts of III possibly were absorbed from the peritoneal cavity because the absorption rate was controlled more by the concentration of dimethyl sulfoxide than by the concentration of III in the cavity.

Varying Both Dose and Solvent Volume—The interrelationship between some doses was not adequately explained by a simple precipitation model alone. Plateaus at very different levels were seen in blood profiles resulting from injection of different volumes of the one solution, *e.g.*, 2.5 mg in 0.25 ml, 5 mg in 0.5 ml, and 10 mg in 1.0 ml of a 10-mg/ml solution of III (Figs. 3, 4, and 5). This result may have been expected if the plateau level was dependent on the dimethyl sulfoxide concentration in the peritoneal fluid and if this concentration was constant after injection. However, if dimethyl sulfoxide was rapidly absorbed, the blood plateau level should have been governed by the saturation concentration of III in the aqueous peritoneal fluid and would have thus been independent of dose or injection volume. In the event of precipitation, however, many additional factors may have influenced the plateau level in the blood profile, factors such as the volume of peritoneal fluid and the relative rates of precipitation, redissolution, and absorption of III.

Injecting Solvent after Dose—It might be proposed that dimethyl sulfoxide improved absorption not by influencing the solubility of III but by some physiological action, *e.g.*, on the peritoneal membrane. Therefore, a 5-mg ip dose of III in 0.5 ml of 60% dimethyl sulfoxide was followed after about 20, 40, 60, 90, or 150 min by an intraperitoneal injection of 1.0 ml of 60% dimethyl sulfoxide (Fig. 6). A peak in the blood curve occurred immediately after the dimethyl sulfoxide "chase" injection, irrespective of the time at which it was given. With the baseline of each peak thus induced, taken as a straight line joining the point immediately (1.5 min) prior to the dimethyl sulfoxide chase with that about 20 min later, the heights of these peaks were expressed as a percentage of the current baseline blood levels (Table I).

Where conventional first-order absorption applies, around 90% of the dose has usually been absorbed by the time maximum blood levels are reached. The initial peak after a 5-mg ip dose of III was almost always observed before 10 min. On fairly conservative grounds then, if normal first-order kinetics had been operating, only 0.0001% of the dose would have remained in the peritoneal cavity 60 min after dosing. It is highly improbable that the stimulation of even complete absorption of this percentage of the original dose could lead to the 17% enhancement ($p < 0.01$) of blood level caused by dimethyl sulfoxide administration 61.5 min after the III dose. While these data are not consistent with a physiological effect of dimethyl sulfoxide on conventional absorption, they confirm the precipitation model that predicts that dimethyl sulfoxide momen-

Table I—Effect of Dimethyl Sulfoxide Solvent Injected after III

Animal	Time of Solvent Injection, min	Time of Peak, min	Enhancement by Solvent Injection, %	
1	21.5	25	6.7	
2	21.5	25	29.6	
3	21.5	25	43.5	
4	21.5	25	32.5	
5	21.5	25	25.9	
6	21.5	25	29.1	
			Mean	27.9
7	41.5	45	29.2	
8	41.5	45	36.8	
			Mean	33.0
9	61.5	65	15.8	
10	61.5	65	13.6	
11	61.5	65	15.5	
12	61.5	65	17.2	
13	61.5	65	20.8	
			Mean	16.6
14	91.5	95	18.4	
15	91.5	95	48.4	
16	91.5	95	17.3	
			Mean	28.0
17	151.5	155	15.2	
18	241.5	250	8.5	
19	241.5	245	5.7	
20	241.5	245	6.9	
21	241.5	245	11.2	
22	241.5	250	10.3	
			Mean	8.5

tarily increases the solubility of precipitated triazine in the peritoneal cavity.

Dimethyl sulfoxide injection 241.5 min after the triazine dose produced significantly less ($p < 0.01$) percentage enhancement of blood levels than did dimethyl sulfoxide 61.5 min after the triazine. A decline with time in the capacity of dimethyl sulfoxide to enhance blood levels of III is not likely if enhancement is due to some systemic (rather than absorptive) physiological action of dimethyl sulfoxide. This decline, however, confirms again the precipitation model that allows that the precipitate in the peritoneal cavity is progressively redissolved and thus provides a diminishing basis for the influence of a secondary dimethyl sulfoxide injection on the blood profile.

Dimethyl sulfoxide (60%) was administered either 61.5 or 121.5 min after dosing five rats with 5 mg ip of II, a water-soluble compound. Minor enhancement of blood II levels was noticed at both times (4.4 and 2.9% after 61.5 min; 0, 5.4, and 10.7% after 121.5 min) but was even less than enhancement of III levels after the 241.5-min dimethyl sulfoxide administration. Moreover, with II, blood level enhancement did not appear to follow dimethyl sulfoxide administration as closely as with III.

DISCUSSION

Of the three aryldihydro-*s*-triazines chosen for study, two were among folate antagonists previously tested (2) for *in vivo* antineoplastic activity; III was reported to be the most effective of a series of long chain substituted phenyldihydrotriazines in prolonging survival of rats bearing Walker 256 ascites tumor; II, without long chain substitution, was a more potent antifolate and inhibitor of L-1210 tumor cultures but, nevertheless, compared very poorly with more complex inhibitors such as III in its *in vivo* antineoplastic efficacy. Since adverse pharmacokinetic properties may have been responsible for the comparative lack of *in vivo* activity by II, the prototype of the series I was included in the present study to provide triazines with molecular weights both lower and higher than that of II.

The relative elimination characteristics of the triazines (3) do not explain the relative inactivity *in vivo* of the more slowly eliminated II. Moreover, in the present study, blood II concentrations were shown to reach five times the concentrations attainable with III and to be more persistent.

The shape of the blood profiles observed after intraperitoneal injection of III indicates that the blood levels attained are comparatively low, largely because of slower absorption. However, action is not required in the bloodstream so much as in the peritoneal cavity which accommodates the Walker 256 tumor in free-cell form. With compounds as rapidly excreted (3) and having as large volumes of distribution as these triazines, it seems unlikely that concentrations in the peritoneal cavity anywhere near those resulting initially from the intraperitoneal injection itself can be achieved or maintained by return of the drug *via* the bloodstream. Thus, the drug level in the blood might be regarded as an index not of the rate of arrival of the drug at its site of action but rather of the rate of its loss from that site. A significant delay in absorption might then confer an advantage for activity.

Simulation of II distribution according to a two-compartment model suggests that only about 1% of an intraperitoneal dose remains in the peritoneal cavity after 30 min (without allowing for return of triazine *via* the bloodstream). On the other hand, after apparent precipitation of III following its intraperitoneal injection, the concentration in peritoneal fluid may, for about 90 min at least, approximate the aqueous saturation level, although unexplained phenomena make the actual concentration uncertain. (Any estimate of peritoneal concentrations from present kinetic information must also be judged speculative.)

Furthermore, although the concentration might commence to decline after 90 min, the precipitate may persist for as long as 240 min (dimethyl sulfoxide chase experiments), leading to less than expected rates of decline between 90 and 240 min. Thus, it seems that precipitation may be a mechanism whereby concentrations well in excess of the ED_{50} (3.8×10^{-6} mg/ml for III against L-1210 cultures) are considerably sustained at the site of action.

As a result of this mechanism, apparently, an intraperitoneal dose of III was effective against peritoneal Walker 256 but not against Walker 256 in the leg muscle (2). Furthermore, all aryldihydrotriazines in this series that were active against Walker 256 ascites were substituted on the phenyl ring with long nonpolar side chains that probably permitted no greater solubility than III. Given intraperitoneally, none was as active against Walker 256 in leg muscle as they were against the ascites tumor.

Equivalent solubility could be expected also from a series of irreversible, isoenzyme-selective inhibitors (identical but bearing a sulfonyl fluoride substituent). These compounds were similarly active against Walker 256 ascites, but their chemotherapeutic indexes did not match their isoenzyme selectivities (2). Since precipitation in the peritoneal cavity might reasonably be expected both to increase antineoplastic efficacy and to decrease systemic toxicity, it should not be surprising that these compounds might have chemotherapeutic indexes reflecting their relative solubilities as much as their relative isoenzyme selectivities.

Two factors complicate these findings. The antineoplastic study (2) employed III as the ethanesulfonate salt, but only the *p*-toluenesulfonate was available during the pharmacokinetic study. In addition, rats used for pharmacokinetic studies did not carry ascites tumors.

Baker and Ashton (12) advanced the desirability of administering III "by intravenous infusion, so that administration could be discontinued at once should toxicity develop." They reported that III (ethanesulfonate) "was not soluble enough to achieve a toxic dose intravenously." Although their findings are not stated in detail, it is inferred that the compound was not only nontoxic but also ineffective by this route (otherwise the sought-after specificity would have been attained). Not only does their statement once again indicate that the antineoplastic activity of III was dependent on the injection route and the tumor sharing the peritoneal cavity but that insolubility was similarly a characteristic with the ethanesulfonate as with the *p*-toluenesulfonate salt of III. In contrast to the ethanesulfonate, the *p*-toluenesulfonate was soluble enough to achieve, as indicated before, a consistently lethal intravenous dose at little more than 4 mg/kg.

It is, nevertheless, difficult to reconcile these observations with the approximate solubility of III ethanesulfonate given by Baker and Ashton (12, 13) at 10 mg/ml (these authors indicated that the solubility given was approximate but did not state how it was determined). At this solubility, a large and surprising discrepancy would exist between the solubilities of the ethanesulfonate and the *p*-toluenesulfonate salts of III, and it is questionable whether precipitation would occur from the volume of peritoneal fluid of an animal bearing an ascites tumor. Solubilities (<0.5–5 mg/ml) given for other triazines effective *in vivo* are consistent with their probable precipitation in the peritoneal cavity, as observed for III *p*-toluenesulfonate.

Data from a precipitating compound are, at this stage, too complex to fit satisfactorily to mathematical models. Preliminary compartmental modeling with soluble I and II, however, indicates that II is absorbed from the peritoneal cavity more slowly than I. If this trend continues toward III and other higher molecular weight triazines, a slower inherent absorption may, in addition to precipitation, contribute to their efficacy against the peritoneal tumor. This slower inherent absorption may be particularly relevant to the antiascites activity of a later series of water-

soluble, but high molecular weight, aryldihydro-*s*-triazines synthesized by Baker and Ashton (12).

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Synthesis, Toxicity, and Cardiovascular Properties of *N*-Aralkyl- and *N*-Acyl-5-aminoethylindans

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Abstract □ Secondary amines and amides of 5-aminoethyl-6-methoxyindan and 5-aminoethyl-6-methylindan were synthesized, and the blood pressure lowering effects and accompanying changes in heart rate were evaluated in the unanesthetized desoxycorticosterone acetate hypertensive rat. The acute toxicities of the compounds were determined in mice. The amines were significantly more potent than the amides as antihypertensive agents and also were more toxic. 5-(3,4-Dimethoxybenzyl)aminoethyl-6-methylindan produced the greatest depression in systolic blood pressure at the dose level studied. Structure–activity relationships relevant to blood pressure lowering, heart rate, and toxicity are discussed.

Keyphrases □ Indans, various substituted—synthesized, cardiovascular properties and toxicity evaluated, rats □ Cardiovascular properties—various substituted indans evaluated □ Toxicity—various substituted indans evaluated □ Structure–activity relationships—various substituted indans evaluated for toxicity and cardiovascular properties

The recent synthesis of cyclopentanoisoquinolines (1, 2) is a continuation of interest in the cardiovascular activity of substituted and reduced isoquinolines (3–6). During the synthesis of the novel cyclopentano[*h*]- and [*f*]-1,2,3,4-tetrahydroisoquinolines (1, 2), some previously unreported substituted aminoethylindans (1) were produced as intermediates to the desired products.

In an attempt to search exhaustively for antihypertensive agents, these intermediates were screened in the desoxycorticosterone acetate hypertensive rat for their blood pressure lowering effects. The hypotensive properties noted with the few intermediates in this screening test prompted preparation of derivatives of the aminoethylindan nucleus in the hope that blood pressure lowering activity might be enhanced and some structure–activity relationships could be developed. This approach was further encouraged by the report of Troxler and Hofmann (7) that certain *N*-substituted aminoethylindans possessed significant hypotensive activity.

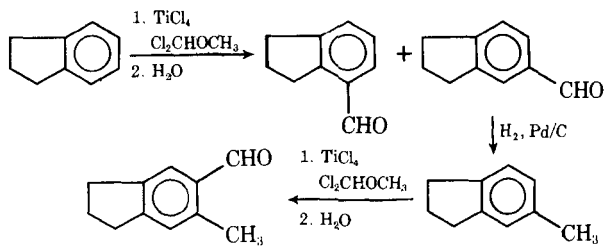
The synthesis of eight compounds is reported here, together with the mouse approximate LD_{50} (ALD_{50}) and the effects of the compounds on systolic blood pressure and heart rate in the hypertensive rat.

EXPERIMENTAL

Chemistry—The synthesis of the precursor molecules (5-aminoethyl-6-methoxyindan and 5-aminoethyl-6-methylindan) for the current series was reported previously in connection with the synthesis of the cyclopentano-1,2,3,4-tetrahydroisoquinolines (1, 2). The amide derivatives were synthesized from the precursor aminoethylindans by the classic acylation with the appropriate acyl chloride in the presence of a base. Compound VIII was prepared from the aminoethylindan by condensation with 3,4-dimethoxybenzaldehyde, followed by catalytic hydrogenation of the resulting Schiff base. The synthetic pathway for the preparation of the compounds is shown in Schemes I–III.

Physical properties and analytical data of the synthesized compounds are shown in Table I. All melting points were determined on a melting-point apparatus[1] and are uncorrected. IR spectra were determined[2] in potassium bromide and were characteristic of the compounds reported. Elemental analyses[3] were within ±0.4% of the theoretical values.

Biological Methods—Acute toxicity determinations were performed in female Swiss-Webster mice, 15–24 g. Compounds were administered



Scheme I

[1] Swissco.

[2] Beckman IR 33.

[3] Galbraith Laboratories, Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz.