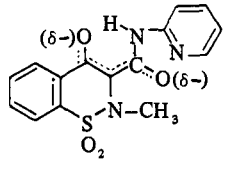
Table I. Relative Antiedema Potencies (Rat) and Plasma Half-Lives (Dog) of N-Heterocyclic Carboxamides of 4-Hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxides

R[a]	Yield, %	Mp, °C	Crystn solvent[b]	Formula	Relative potency[c]	Plasma half-life, hr[d]
2-Thiazolyl (sudoxicam)	78	256	X	$C_{13}H_{11}N_3O_4S_2$	2.9	60
4,5-Dimethyl-2-thiazolyl	87	234	X	$C_{15}H_{15}N_3O_4S_2$	1.6	53
2-Pyridyl	45	200	M	$C_{15}H_{13}N_3O_4S$	1.6	40
6-Methyl-2-pyridyl	62	191	X	$C_{16}H_{15}N_3O_4S$	0.6	12
Indomethacin					1.0	0.3[e]

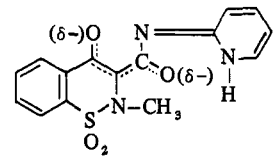
[a] See structure II. Analyses for C, H, N for all compounds were within ±0.4% of the theoretical values. [b] X = xylene; M = methanol. [c] Potency determined by dose-response comparisons at four dose levels for each drug. Edema was induced by subplantar administration of carrageenan to the rat; drugs administered po 1 hr before, and edema measurement 3 hr after, injection of carrageenan. [d] Drugs administered intravenously (10 mg/kg); assay of drug in plasma samples by extraction and measurement of optical density at 270 and 360 mμ in a Beckman DU spectrophotometer. [e] Ref 9.

amides of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide. In the latter compounds,[4] and in the dioxoisoquinolines,[1] contributions from structures III and IV to stabilization of the enolate ion were suggested to explain the greatly enhanced acidity of these β-ketocarboxamides.

We would now like to suggest that for the present compounds, in addition to V (illustrated by the *N*-(2-pyridyl)carboxamide), contributions from the tautomeric structure VI may impart further stability to the enolate



V



VI

anion. Such stabilization of the enolate ion would thereby contribute to a further increase in the acidity of the conjugate acids.

Biological Data. The N-heterocyclic carboxamides of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide exhibit potent antiinflammatory activity when administered orally in the carrageenan-induced paw edema test,[6] as performed in both normal and bilaterally adrenalectomized rats (Table I). In this test, sudoxicam (II, R = 2 thiazolyl) was 2.9 times more potent than indomethacin with dose-response curves for each drug being linear and parallel. In addition, sudoxicam has displayed potent antiinflammatory activity in inhibiting the erythema induced by ultraviolet irradiation in the guinea pig,[7] suppressing granulation tissue formation around an implanted irritant[2] and ameliorating the symptoms of arthritis induced by adjuvant.[8] The oral LD_{50} of sudoxicam is 260 mg/kg in mice and 157 mg/kg in rats with death occurring only after 3 days. Chronic administration (3 months) of sudoxicam to rats (5 mg/kg daily) and monkeys (10 mg/kg daily) induced no pathological changes (Drs. E. J. Gralla and R. B. Stebbins of these laboratories).

Rapid transport of a potentially useful drug to the site of inflammation, as well as the attainment and maintenance of effective drug concentrations at that site, contributes in a large degree to the determination of the therapeutic utility of a drug. It was therefore of interest that the more potent compounds in this series were rapidly absorbed after oral administration and also possessed extended half-lives in the dog (Table I). Furthermore, sudoxicam has an extended plasma half-life in man; depending on the plasma concentration, this half-life declines continuously from about 96 hr (at plasma concentrations >20 μg/ml) to about 24 hr (at plasma concentrations <2 μg/ml).[10] Clinical evaluation of sudoxicam is proceeding.

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Antineoplastic Activity of 6-Dimethylaminonicotinamide†

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Abnormally high levels of tRNA methyltransferase enzymes as well as methylase activity in a number of neoplastic tissues (including virally induced, chemically induced, and spontaneous tumors) have been attributed to the lack of methylase inhibitors[1] (which are present in normal cells). A recent study[2] on the inhibition of tRNA methyltransferase activity revealed that nicotinamide (Ia) was found to be one of those long-sought inhibitors. This report is of extreme interest and logical since, metabolically, nicotinamide is readily formed from DPN and TPN *in vivo* and is therefore abundant in normal cells.

Although only tRNA methyltransferase inhibitory rather than antitumor activity for nicotinamide and several structural analogs of nicotinamide (*e.g.*, thionicotinamide (Ib), 6-aminonicotinamide (Ic), and pyridine-3-carboxaldehyde) was reported,[2] another simple nicotinamide analog prepared in this laboratory some years ago was found to possess antineoplastic activity against several experimental tumor systems. We wish to present the test data in the present

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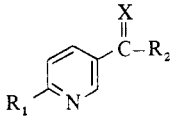
Table I. Antineoplastic Screening Results of Nicotinamide Derivatives[a]

Compd	Dose,[b] mg/kg	Test/control FV	LE	LL	P4	SA	WM	Cell culture ED_{50},[c] μg/ml
Ie	150.0		125					
	100.0		126					
	66.0		127					
	45.0		120					
	16.0					48		
	13.0	9	106					
	10.0						86	
	8.0	23						
	6.0	30		36	130			
	4.0	48[d]						
	3.0	41		63	123			
	1.5			100	115			
								$>1.0\times10^2$ (KB)
If	31.0					25		
	25.0							
	12.5		116				81	
								$>1.0\times10^2$ (KB)

[a] The biological screening was performed by the screening contractors of National Cancer Institute. FV = solid Friend virus leukemia, LE = lymphoid leukemia L1210, LL = Lewis lung carcinoma, P4 = P1534 leukemia, SA = sarcoma 180, WM = Walker 256 (intramuscular), KB = human epidermoid carcinoma of the nasopharynx. [b] Below toxicity level. [c] ED_{50} = the dose that inhibits growth to 50% of control growth. [d] Cures 3/10.

communication and to substantiate the claim of Buch and coworkers[2] that certain nicotinamide analogs may possess antitumor activity.



Ia, $R_1 = H$; $R_2 = NH_2$; X = O
b, $R_1 = H$; $R_2 = NH_2$; X = S
c, $R_1 = NH_2$; $R_2 = NH_2$; X = O
d, $R_1 = H$; $R_2 = H$; X = O
e, $R_1 = N(CH_3)_2$; $R_2 = NH_2$; X = O
f, $R_1 = NHCH_3$; $R_2 = NHCH_3$; X = O

6-Dimethylaminonicotinamide (Ie, NSC-73291), prepared by the treatment of 6-chloronicotinamide with dimethylamine in aqueous ethanol, was found to possess confirmed activity in sequential testing against the Friend virus transplantable tumor, borderline activity against Lewis lung carcinoma, leukemias L1210 and P1534, and no activity against sarcoma 180, Walker carcinosarcoma 256, and KB cell culture. Available test results of the corresponding monomethylated analog, *N*-methyl-6-(methylamino)nicotinamide[3] (If, NSC-94489), are also reported (see Table I). These data suggest that properly designed analogs of nicotinamide derivatives should provide compounds with interesting biological activity.

The exact mode of action of nicotinamide in tRNA methyltransferase inhibition is not yet known. A recent report that another pyridine derivative, pyridoxal 5′-phosphate, is an *in vitro* inhibitor of catechol-*O*-methyltransferase (COMT),[4] together with the postulation of the relationship between COMT and tRNA *O*-methyltransferase,[1] suggests that nicotinamide derivatives may also act as inhibitors of tRNA *O*-methyltransferases. Some *in vitro* inhibitory studies of these compounds against both normal and tumor tRNA methyltransferase enzymes would therefore be of interest.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

6-Dimethylaminonicotinamide (Ie). A suspension of 10 g (0.064 mole) of 6-chloronicotinamide and 150 ml of 25% aqueous dimethylamine (0.83 mole) in 20 ml of ethanol was refluxed for 10 min. The resulting solution deposited, on cooling, 9 g (85% yield) of analytically pure pale yellow crystals, mp 224–226°. *Anal.* ($C_8H_{11}N_3O$) C, H, N.

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2-Phenyl-4*H*-cyclopentathiazole-4-carboxylic Acids as Potential Antiinflammatory Agents

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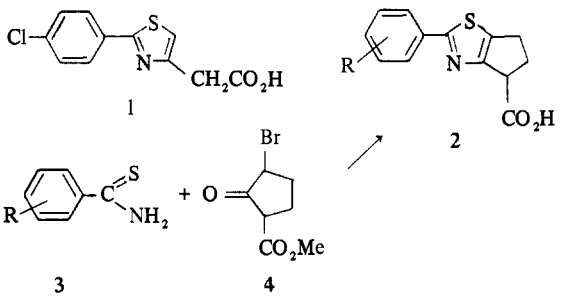
Reports of the antiinflammatory activity of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid[1] and *p*-isobutylphenylacetic acid[2] have stimulated the preparation of a variety of heterocyclic and arylalkanoic acids for testing as potentially useful antiinflammatory agents. Certain aryl-substituted thiazoleacetic acids have received considerable attention,[3,4] and 2-(*p*-chlorophenyl)thiazol-4-ylacetic acid (1) is exemplary of this class. Activity in adjuvant-induced arthritis in rats,[5] carrageenin-induced edema in rats,[6] and ultraviolet-induced erythema in guinea pigs[7] has been reported for compound 1.[4] Moreover, the compound is also effective against the writhing syndrome in mice and in the suppression of body temperature increases induced by injection of a bacterial pyrogen into rats.[4] Because of this profile of antiinflammatory, analgetic, and antipyretic properties, we prepared a series of 2-(substituted phenyl)-4*H*-cyclopentathiazole-4-carboxylic acids (2) for testing as potential antiinflammatory agents.



The desired 2-phenyl-4*H*-cyclopentathiazole-4-carboxylic acids (2) (R = H, *p*-Cl, *m*-CH_3, *m*-CF_3) were prepared by condensation of the appropriate thiobenzamide 3 with methyl 3-bromo-2-oxocyclopentanecarboxylate (4)[8] and saponification of the resulting product. The ultraviolet and nmr spectra of the cyclopentathiazolecarboxylic acids 2 support the assigned structures. In particular, the position