ol-induced seizures are shown in Table II. All nitrobenzamides exhibited protection which ranged from 20 to 60%. Nitrobenzamides having 3-methylphenyl and 2-methoxyphenyl substituents (**3, 6, 10, 13**) at position 1 of the thiocarbamide moiety in both 3-nitro- as well as 4-nitrobenzamides were found to exhibit 60% protection against pentylenetetrazol-induced seizures. It is evident from Table II that all 3-nitrobenzamides elicited low mortalities after 24 hr in pentylenetetrazol-treated animals.

It is evident from Table III all nitrobenzamides were found to inhibit *in vitro* NAD-dependent oxidation of pyruvate, α-ketoglutarate, and β-hydroxybutyrate when they were incubated with rat brain homogenate. Selectivity of inhibition of respiratory activity was thus observed since NAD-independent oxidation of sodium succinate was found to remain unaltered. The ability of these nitrobenzamides to inhibit the oxidation of $NADH_2$ unlike anticonvulsant quinazolones[6,7] provides evidence regarding their possible inactivation of the process of electron transfer in the electron transport chain (ETC) by presumably acting at the site of transfer of electrons from $NADH_2$ to FAD.

The position of the nitro substituent at either the 3 or 4 position of the benzamide nucleus was found to have no significant effect on the biological properties of the compounds. On the other hand, substitutions at various positions of the benzamide and at position 1 of the thiocarbamide moiety have been found to play a definite role in influencing the ability of these compounds to inhibit oxidations of pyruvate, α-ketoglutarate, β-hydroxybutyrate, and $NADH_2$. In all these nitrobenzamides presence of a 3,4-dimethylphenyl substituent was found to be most effective in producing inhibition of the oxidation of pyruvate, α-ketoglutarate, β-hydroxybutyrate, and $NADH_2$ independently while an unsubstituted phenyl group was found to exhibit low inhibitory effect under similar experimental conditions. The greater effectiveness of 3-nitro- as well as 4-nitrobenzamides having 3-methylphenyl and 2-methoxyphenyl substituents at position 1 of the thiocarbamide moiety could not be reflected by their ability to selectively inhibit NAD-dependent oxidations. Introduction of a Me or MeO substituent in the phenyl moiety of the thiocarbamide part resulted in an increase in the degree of inhibition which was in the order of 4-substituted > 3-substituted > 2-substituted > unsubstituted. It was interesting to note that, in general, substitution of a MeO group (**6, 7, 13, 14**) for a Me group (**2, 4, 9, 11**) at position 2 or 4 of the phenyl nucleus attached at position 1 of the thiocarbamide moiety was found to decrease the inhibitory ability of almost all of these 3-nitro- and 4-nitrobenzamides (Table III). Inhibition, on the other hand, was found to increase by substitution of methoxy groups (**6**) in place of methyl substituents (**5**), which increase, however, remains unexplained on the basis of these observations. These studies, in spite of exhibiting selective inhibition of NAD-dependent oxidations, have failed to reveal a biochemical basis for anticonvulsant properties of these substituted nitrobenzamides.

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Sudoxicam and Related N-Heterocyclic Carboxamides of 4-Hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide. Potent Nonsteroidal Antiinflammatory Agents

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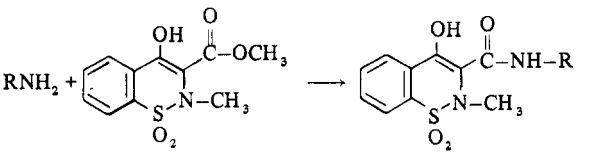
Previous publications from these laboratories have described the antiinflammatory properties in animals of acidic heterocyclic compounds containing, as essential structural features, a relatively nonbasic nitrogen atom, a potentially enolic function, and a carboxamide substituent. Our initial reports described the antiinflammatory activity of the carboxanilides of 1,3-dioxoisoquinoline,[1,2] of 3-oxo-1,2-benzothiazine 1,1-dioxide,[3] and of 4-hydroxy-1,2-benzothiazine 1,1-dioxide.[4,5] These compounds generally exhibited potencies in the range of that of phenylbutazone. We report here the synthesis and biological properties of some N-heterocyclic carboxamides of the 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide system, some of which exhibit extended plasma half-lives in animals and man and antiinflammatory activity in animals exceeding that of indomethacin.

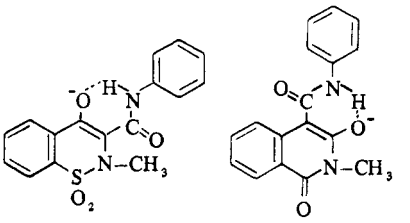
Discussion

The N-heterocyclic carboxamides were made in good yields from 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide[4] (I) and the ap-



I II

propriate heterocyclic amine in refluxing (18 hr) xylene solution. Infrared and nuclear magnetic resonance spectra of II indicated predominance of the enol rather than the



III IV

β-keto form. These N-heterocyclic carboxamides were generally more acidic ($pK_a \sim 5$-6 in 2:1 dioxane-H_2O) than the previously studied[4] N-aryl and N-alkyl carbox-

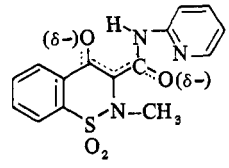
Table I. Relative Antiedema Potencies (Rat) and Plasma Half-Lives (Dog) of N-Heterocyclic Carboxamides of 4-Hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxides

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]

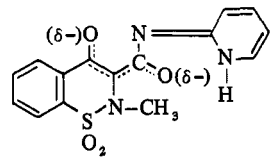
[a] See structure II. Analyses for C, H, N for all compounds were within ±0.4% of the theoretical values. [b] X = xylene; M = methanol. [c] Potency determined by dose-response comparisons at four dose levels for each drug. Edema was induced by subplantar administration of carrageenan to the rat; drugs 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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