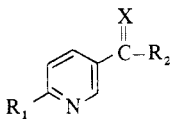
Table I. Antineoplastic Screening Results of Nicotinamide Derivatives[a]

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.



la, 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.

References

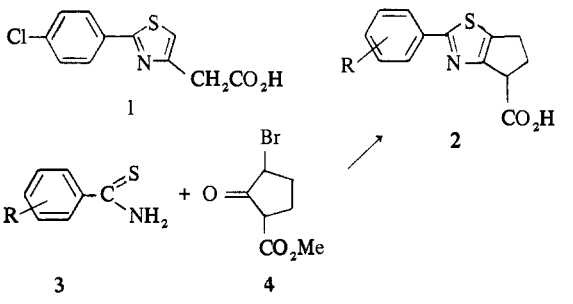
(1) C. C. Cheng, *J. Pharm. Sci.*, 61, 645 (1972), and references cited therein.
(2) L. Buch, D. Streeter, R. M. Halpern, L. N. Simon, M. G. Stout, and R. A. Smith, *Biochemistry*, 11, 393 (1972).
(3) A. Lendle, German Patent 817,911 (1951); *Chem. Abstr.*, **52**, 2087*g* (1958).
(4) I. B. Black, *Biochem. Pharmacol.*, **20**, 924 (1971).

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

Francis J. McEvoy and George R. Allen, Jr.*

Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965. *Received January 3, 1972.*

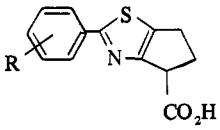
Reports of the antiinflammatory activity of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid[1] and *p*-isobutylphenylacetic acid[2] have stimulated the preparation of a variety of heterocyclic and arylalkanoic acids for testing as potentially useful antiinflammatory agents. Certain aryl-substituted 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.



1 2 3 4

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

Table I. 2-Phenyl-4*H*-cyclopentathiazole-4-carboxylic Acid and Congeners



No.	Compound	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
2a	2-Phenyl-4*H*-cyclopentathiazole-4-carboxylic acid	H	45	Acetone–hexane	210–212	$C_{13}H_{11}NO_2S$	C, H, N, S
2b	2-(*p*-Chlorophenyl)-4*H*-cyclopentathiazole-4-carboxylic acid	*p*-Cl	58	Acetone	210–211	$C_{13}H_{10}ClNO_2S$	C, H, N, S, Cl
2c	2-(*m*-Tolyl)-4*H*-cyclopentathiazole-4-carboxylic acid	*m*-CH_3	37	Acetone–hexane	147–148	$C_{14}H_{13}NO_2S$	C, H, N, S
2d	2-(*m*-Trifluoromethylphenyl)-4*H*-cyclopentathiazole-4-carboxylic acid	*m*-CF_3	41	Acetone–hexane	149–150	$C_{14}H_{10}F_3NO_2S$	C, H, N, S, F

of maximum absorption (308–313 mμ) in the ultraviolet region is in harmony with the presence of the 2-phenylthiazole chromophore.† Moreover, the chemical shift (δ 3.97–4.12) of the 4-proton is consistent with that of a proton in a doubly allylic environment.

When administered in doses of 250 mg/kg the 2-phenyl-4*H*-cyclopentathiazole-4-carboxylic acids **2b–2d** failed to suppress carrageenin-induced edema in rats and ultraviolet-induced erythema in guinea pigs. Similarly, these compounds were without effect at 50 mg/kg per day against adjuvant-induced arthritis in rats. Aspirin is accepted as active in these assays at the indicated doses with a 99% frequency, and the thiazolylacetic acid **1** is active at these screening levels. Compound **2a** was ineffective in the carrageenin edema and uv erythema assays, but exhibited a marginal effect on the primary lesions of adjuvant-induced arthritis; however, **2a** proved toxic at levels of 100 mg/kg per day in this assay.‡

Experimental Section

General. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Solutions were dried ($MgSO_4$) and concd under reduced pressure on a rotary evaporator. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. The petr ether used was that fraction with bp 30–60°.

Methyl 3-Bromo-2-oxocyclopentanecarboxylate (4). This substance was prepared in 47% yield as described previously.[8] It had bp 97–103° (1.77 mm); λ_{max} 263 mμ (ε 5300); ν^{neat} 1764, 1730, 1672, 1629 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.90–2.80 (m, 4, CH_2CH_2), 3.47 (m, <1, 1-H in the keto form), 4.07–4.54 (m, <1, 3-H in the keto form), 4.74–5.04 (m, <1, 3-H in the enol form).[9]

Preparation of the 2-Phenyl-4*H*-cyclopentathiazole-4-carboxylic Acids. The following preparation illustrates the general procedure. A solution of 1.37 g (10 mmoles) of thiobenzamide and 2.65 g (12 mmoles) of methyl 3-bromo-2-oxocyclopentanecarboxylate in 30 ml of EtOH was stirred at reflux temperature for 2 hr. The solvent was removed, and the residue was distributed between EtOAc and 10% NaOH soln. The organic layer was washed successively with 10% NaOH soln and H_2O, dried, and evaporated to give 2.56 g of an oil. This material was treated with 33 ml of 10% NaOH soln at reflux temperature for 1 hr. The solution was diluted with 125 ml of boiling H_2O, treated with activated charcoal, and filtered. The cooled filtrate was acidified by addition of 5 ml of concl HCl and then HOAc. The precipitated solid was collected, washed with H_2O, and dried to give 1.11 g of 2-phenyl-4*H*-cyclopentathiazole-4-carboxylic acid, mp 201–205°. The purification and characterization of this material is summarized in Table I. The pertinant spectral properties are given in the discussion.

Acknowledgment. The authors are indebted to Dr. K. Bernady for the generous gift of methyl 2-oxocyclopentanecarboxylate which made this investigation possible. Microanalyses were furnished by Mr. L. Brancone and his staff and spectral measurements were supplied by Mr. W. Fulmor and his associates.

References

(1) T. Y. Shen, T. B. Windholz, A. Rosegay, B. E. Witzel, A. N. Wilson, J. D. Willett, W. J. Holtz, R. L. Ellis, A. R. Matzuk, S. Lucas, C. H. Stammer, F. W. Holy, L. H. Sarrett, E. A. Risley, G. W. Guss, and C. A. Winter, *J. Amer. Chem. Soc.*, 85, 488 (1963).
(2) S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholson, *Nature (London)*, 200, 271 (1963).
(3) K. Brown, J. F. Cavalla, D. Green, and A. B. Wilson, *ibid.*, 219, 164 (1968).
(4) W. Hepworth, B. B. Newbould, D. S. Platt, and G. J. Stacey, *ibid.*, 221, 582 (1969).
(5) B. B. Newbould, *Brit. J. Pharmacol. Chemother.*, 21, 127 (1963).
(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).
(7) C. V. Winder, J. Wax, V. Burr, M. Been, and C. E. Rosiere, *Arch. Int. Pharmacodyn. Ther.*, 116, 261 (1958).
(8) B. A. Zaputryaev, A. M. Khaletskii, and L. D. Pimenova, *Zh. Obshch. Khim.*, 31, 737 (1961); *Chem. Abstr.*, 55, 23370e (1961).
(9) S. J. Rhoades, *J. Org. Chem.*, 31, 171 (1966).

†Compound **1** exhibits maximum absorption at 298 mμ (ε 17,000).

‡Private communication from Dr. A. E. Sloboda.

Synthesis and Central Nervous System Depressant Activity of New Oxaza Heterocyclic Amides

G. Pifferi,* P. Consonni, A. Diena, and B. Rosselli Del Turco

Research Laboratories, Gruppo Lepetit S.p.A., Milan, Italy.
Received November 29, 1971

Various types of trimethoxybenzamides and trimethoxycinnamides of heterocyclic amines have been investigated[1-8] since one of them, the morpholide I, was found to possess an interesting tranquilizing activity, free from any muscle-relaxant effect.[9-11] By varying the amine moiety in I,

*Author to whom correspondence should be addressed at the Research Laboratories I.S.F., Italseber, Milan, Italy.