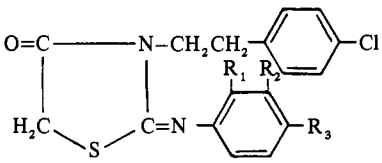
Table III. Effect of 2-Arylimino-3-(*p*-chlorophenethyl)thiazolid-4-ones on the Oxidation of Different Substrates of Tricarboxylic Acid Cycle and β-Hydroxybutyrate by Rat Brain Homogenate[a]



			Pyruvate					
R_1	R_2	R_3	$-NAD^+$	$+NAD^+$	β-Hydroxy-butyrate	Citrate	α-Keto glutarate	Succinate
H	H	H	54.73 ± 0.54	42.15 ± 0.68	53.98 ± 0.84	53.05 ± 0.85	65.12 ± 0.93	Nil
H	CH_3	H	50.04 ± 0.67	36.15 ± 0.90	49.42 ± 0.78	47.93 ± 0.84	62.18 ± 0.61	Nil
H	H	CH_3	47.48 ± 0.81	41.32 ± 0.82	46.33 ± 0.89	50.14 ± 0.76	58.43 ± 0.98	Nil
H	CH_3	CH_3	49.78 ± 0.92	32.21 ± 0.84	44.10 ± 0.67	43.87 ± 0.78	56.82 ± 0.90	Nil
OCH_3	H	H	32.75 ± 1.00	26.44 ± 0.98	33.20 ± 0.54	28.12 ± 0.92	34.10 ± 0.85	Nil

[a]The O_2 uptake was measured at 10-min intervals. The reaction mixt (in a total vol of 3 ml) contains 6.7 m*M* $MgSO_4$, 20 m*M* Na_2HPO_4 in a buffer sol of pH 7.4, 2 m*M* adenylic acid (Na salt) 33 m*M* KCl and 500 μg of cytochrome *c*. The percentage inhibition was calcd from the decrease in O_2 uptake per hr per 100 mg wet wt. The final concn of substrates and 4-thiazolidones were 10 m*M* and 1 m*M*, resp. NAD^+ was used at a final concn of 0.5 m*M*.

evidence that thiazolidones inhibit the oxidative processes where participation of NAD is a limiting factor. At present it is not yet possible to define their exact site of action.

The anticonvulsant activity exhibited by substituted thiazolidones at 100 mg/kg is shown in Table II. All thiazolidones were able to afford protection which, however, was not of a high order. Anticonvulsant activity of these thiazolidones ranged from 20 to 40%, compounds having a Me substituent at the R_3 position of the Ph moiety exhibiting maximum anticonvulsant activity of 40%. The low toxicities of these compounds were reflected by high values of their approximate LD_{50} which in 3 of these thiazolidones was either 1600 mg/kg or higher. In the present investigation no definite correlation could be observed between the anticonvulsant property exhibited by these thiazolidones and their ability to inhibit NAD-dependent oxidations of the substrates of the tricarboxylic acid cycle as well as of β-hydroxybutyrate. These results have also failed to show structure-activity relationships of these thiazolidones with respect to their anticonvulsant or enzyme inhibitory properties.

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Substituted Thiazolylureas

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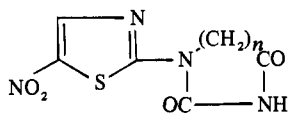
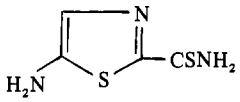
2-Amino-5-nitrothiazole derivatives are known to exhibit antiamebic,[1] antihistomonal,[2] antitrichomonal,[3] and antischistosomal[4] activities. Recently the preparation of some 1-(5-nitro-2-thiazolyl)hydantoins and -hydrouracils (I) possessing antibacterial and antiparasitic activity has been described.[5]



I; *n* = 1-2



II

This note describes the synthesis of some (5-substituted-2-thiazolyl)acylureas (III) (Table I) and -hydrouracils (V) (Table III) from the corresponding 5-substituted-2-aminothiazoles, and also some acylureas (IV) (Table II) and hydantoins from 5-aminothio-2-thiazolecarboxamide (chrysean) (II). The preparation of acylureas from aminothiazoles and acyl isocyanates and cyclization of the appropriate (2- or 3-haloacyl)ureas to the hydantoin or hydrouracil with NaH in DMF are described below.

Experimental Section†

The physical properties of the compds prepd are collected in Tables I-III.

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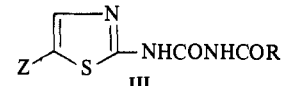
†Melting points are corrected and were determined in a capillary tube. Analytical results were obtained for C, H, and N for all compounds, and, unless otherwise stated, were within ±0.4% of the theoretical values.

Table I. 1-Acyl-3-(5-substituted-2-thiazolyl)ureas

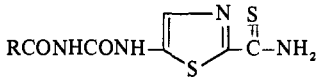


III

Compd	Z[g]	R[h]	Mp, °C	Recrystn solvent[a]	Yield, %	Formula
1	Br	$(CH_2)_2Br$	191	A	27	$C_7H_7Br_2N_3O_2S$
2	Br	Et	209-210	B	67	$C_7H_8BrN_3O_2S$
3	Br	$CHCl_2$	157-158	B	30	$C_6H_4BrCl_2N_3O_2S$
4	I	$(CH_2)_2Br$	179-180 dec	A	41	$C_7H_7BrIN_3O_2S$
5	I	CH_2Cl	197 dec	A	21	$C_6H_5ClIN_3O_2S$
6	$CONH_2$	$(CH_2)_2Br$	>210 dec[b]	A	90	$C_8H_9BrN_4O_3S$[e]
7[c]	$Br(CH_2)_2CONHCONH-p-C_6H_4SO_2$	$(CH_2)_2Br$	233-234 dec	C	33	$C_{17}H_{17}Br_2N_5O_6S_2$[f]
8	CO_2Me	CH_2Cl	192-193 dec	D	45	$C_8H_8ClN_3O_4S$
9	CO_2Me	$(CH_2)_2Br$	225 dec[d]	C-D	79	$C_9H_{10}BrN_3O_4S$
10	$CH_3CONH-p-C_6H_4SO_2$	$(CH_2)_2Br$	230-231 dec	E	30	$C_{15}H_{15}BrN_4O_5S_2$
11	$CH_3CONH-p-C_6H_4SO_2$	$CHCl_2$	233-235 dec	F	42	$C_{14}H_{12}Cl_2N_4O_5S_2$
12	$CH_3CONH-p-C_6H_4SO_2$	CH_2Cl	225-226 dec	A	34	$C_{14}H_{13}ClN_4O_5S_2$
13	$CH_3CONH-p-C_6H_4SO_2$	Et	278-280 dec	A	43	$C_{15}H_{16}N_4O_5S_2$
14	$H_2NSO_2-p-C_6H_4N{=}N$	$(CH_2)_2Br$	246-250 dec	G	18	$C_{13}H_{13}BrN_6O_4S_2$
15	$H_2NSO_2-p-C_6H_4N{=}N$	$CHCl_2$	>360	A	21	$C_{12}H_{10}Cl_2N_6O_4S_2$

[a]A, EtOH; B, 50% AcOH; C, DMF; D, MeOH; E, 50% aq DMF; F, aq EtOH; G, AcOH. [b]Depends on rate of heating; effervesces *ca.* 140-190°. [c]From 2-amino-5-sulfanilylthiazole and 2 moles of 3 bromopropionyl isocyanate. Reaction between the thiazole and 1 mole of isocyanate (giving compound 26) is described in the Experimental Section. [d]Softens *ca.* 185°. [e]C: calcd, 29.9; found, 30.4. H: calcd, 2.8; found, 3.3. [f]C: calcd, 33.4; found, 34.0. [g]2-Amino-5-Z-thiazoles were prepd by the following methods: Z = Br and I [Y. Garreau, *Bull. Soc. Chim. Fr.*, 1048 (1954)]; $CONH_2$ and CO_2Me [H. E. Faith, *J. Amer. Chem. Soc.*, 74, 5799 (1952)]; p-$NH_2C_6H_4SO_2$ and p-$AcNHC_6H_4SO_2$ [R. Dahlbom and T. Ekstrand, *Svensk Kem. Tids.*, 57, 229 (1945)]; and p-$H_2NSO_2C_6H_4N{=}N$ [H. Beyer and G. Wolter, *Chem. Ber.*, 85, 1077 (1952)]. [h]RCONCO were prepd as follows: R = $BrCH_2CH_2$ [H. W. Johnson and D. E. Bublitz, *J. Amer. Chem. Soc.*, 80, 3150 (1958)]; Et [by method of A. J. Hill and W. M. Degnan, *ibid.*, 62, 1595 (1940)]; and $CHCl_2$ and CH_2Cl [A. J. Speziale and L. R. Smith, *J. Org. Chem.*, 27, 3742 (1962)].

Table II. 1-Acyl-3-(2-thiocarbamoyl-5-thiazolyl)ureas



IV

Compd	R	Mp, °C[a]	Yield, %	Formula
16	$(CH_2)_2Br$	345-349 dec	24	$C_8H_9BrN_4O_2S_2$
17	Et	260-261 dec	53	$C_8H_{10}N_4O_2S_2$
18	CH_2Cl	>360[b]	51	$C_7H_7ClN_4O_2S_2 \cdot H_2O$

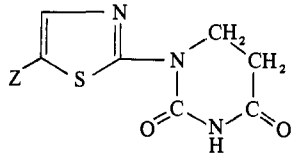
[a]After recrystn from DMF, followed by hot H_2O wash. [b]Sinters >250°.

temp until neutral (1-3 hr), and then poured into H_2O. The solid was collected, washed (H_2O), and recrystd (products listed in Table III).

Similarly, cyclization of 16 furnished 1-(2-thiocarbamoyl-5-thiazolyl)hydrouracil‡ (24) (55%), mp 360° (from DMF–Et_2O) [*Anal.* ($C_8H_8N_4O_2S_2$) C, H, N], and cyclization of 18 provided 1-(2-thiocarbamoyl-5-thiazolyl)hydantoin (25) (39%), mp > 360° (from DMF) [*Anal.* ($C_7H_6N_4O_2S_2$) C, H, N].

1-[p-[(2-Amino-5-thiazolyl)sulfonyl]phenyl]-3-(3-bromopropionyl)urea (26). Treatment of 2-amino-5-sulfanilylthiazole with 1.0 mole of 3-bromopropionyl isocyanate for 2 hr at room temp afforded the title compd (26) (64%), mp 277-278° dec (from 50% AcOH). *Anal.* ($C_{13}H_{13}BrN_4O_4S_2$). C, H, N.

Table III. 1-(5-Substituted-2-thiazolyl)hydrouracils



V

Compd	Z	Mp, °C	Recrystn solvent[a]	Yield, %	Starting compd	Formula
19	CO_2Me	302-304 dec	A	86	9	$C_9H_9N_3O_4S$
20	$CONH_2$	333-334 dec	A	57	6	$C_8H_8N_4O_3S$
21	Br	241 dec	B	36	1	$C_7H_6BrN_3O_2S$
22	I	251-252	C	53	4	$C_7H_6IN_3O_2S$[b]
23	$CH_3CONH-p-C_6H_4SO_2$	291-293 dec	B	62	10	$C_{15}H_{14}N_4O_5S_2$

[a]A, DMF; B, EtOH; C, AcOH. [b]C: calcd, 26.0; found, 26.5.

1-Acyl-3-(2- or 5-thiazolyl)ureas (Tables I and II, Respectively). A soln of the acyl isocyanate (0.033 mole) in THF (5 ml) was added dropwise to a soln of the aminothiazole (0.03 mole) in THF (80 ml), and the mixt was then stirred at room temp for 1-4 hr. The product was filtered off, washed with Et_2O, and recrystd.

Cyclization of 1-(3-Bromopropionyl)-3-(5-substituted-2-thiazolyl)ureas. NaH (50% dispersion in oil; 0.01 mole) was added in portions to a stirred soln of the bromopropionylurea (Table I) (0.01 mole) in DMF (45 ml), and the mixt was stirred at room

Biological Results. None of the thiazoles listed above appeared to have any activity against *Trichomonas vaginalis in vitro*[6] or *Schistosoma mansoni* in mice[7] when tested by methods described previously. Compd 14 had a minimum inhibitory concentration[8]

‡*Chemical Abstracts* nomenclature for 24 and 25 is 5-[tetrahydro-2,4-dioxo-1(2*H*)-pyrimidinyl]thio-2-thiazolecarboxamide, and 5-(2,4-dioxo-1-imidazolidinyl)thio-2-thiazolecarboxamide, respectively.

of 10 μg/ml against *Streptococcus pyogenes*, and this was the only derivative to show activity against a range of bacteria. Against *Entamoeba histolytica*,[6] 1 and 4 were slightly active, causing 90–99.9% inhibition at 10 and 40 μg/ml, respectively. It can be seen from the above results that replacement of the 5-NO_2 group by other electron-withdrawing groups eliminates the antibacterial and antiparasitic activity present in a variety of substituted 2-amino-5-nitrothiazoles.

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Antiviral Benzimidazoles. Direct 1-Substitution of 2-(α-Hydroxybenzyl)benzimidazole and Related Compounds

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Simple 1-alkyl derivatives of 2-(α-hydroxybenzyl)benzimidazole (HBB) and of its *O*-methyl derivative (MBB) are potent inhibitors of the multiplication of several small RNA viruses.[1-4] These derivatives were previously prepared by condensing the appropriately N-substituted *o*-phenylenediamine with mandelic acid[1] or with α-methoxyphenylacetic acid.[2] The diamines had to be synthesized from *o*-chloronitrobenzene. Reaction of the parent HBB or MBB with an alkyl halide and NaOEt in boiling PhMe provides an easier route to many such compounds and also permits synthesis of new highly active compounds, not otherwise readily accessible, and of compounds with ^{14}C- or ^{3}H-labeled 1-alkyl substituents of value in studies of the mechanism of the antiviral action.

Unsuccessful attempts were made to N-alkylate HBB by allowing its Ag salt to react with *n*-PrI using the method of Buchanan, *et al.*[5] Wagner and associates[6] N-methylated a derivative of HBB using MeI, but our attempts to produce a reaction between HBB and PrI under similar conditions failed to give the 1-Pr derivative (PHBB). The yield of PHBB was poor when the reaction was carried out in the presence of NaOEt in boiling EtOH, but was satisfactory in boiling PhMe (Table I).

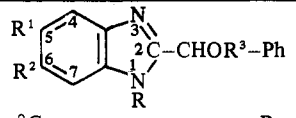
The presence of a substituent in position 4(7) or in position 5(6) of HBB could give rise to 2 isomeric products on N-alkylation. 1-Propylation of 5-chloro-HBB gave both, but the yield of the 5-chloro-1-propyl derivative was much better than that of its 6-chloro isomer. As the former had been previously synthesized by an unambiguous route,[7] the correct structures could be assigned.

Crotyl chloride of bp 84° was used to prepare 1-crotyl-HBB, the structure of the 1 substituent being confirmed by the nmr spectrum and by hydrogenation.

An attempt to prepare L-PHBB by treating L-HBB with PrI in the presence of NaOEt in PhMe gave a crystalline product of the expected formula, but with $[\alpha]^{21}D$ −24.7° (EtOH, *c* 0.77). As D-PHBB has $[\alpha]^{24}D$ + 144° (EtOH, *c* 0.83), the product contd 83% of racemate.

Reactivity of the NH Group. We found that HBB, unlike benzimidazole itself, does not react within 24 hr at 20° either with CH_2O in MeOH (with or without K_2CO_3) or with 2-chloroethanol in the presence of NaOEt in EtOH. The Mannich reaction produces ready substitution at the NH of benzimidazole, but 2-hydroxyphenyl- and 2-hydroxybenzylbenzimidazoles are not attacked at this position.[8] Reaction of the chloromercury derivative of benzimidazole with triacetyl-α-D-ribofuranosyl chloride results in a Walden inversion and the formation, after hydrolysis, of 1-β-D-ribofuranosylbenzimidazole.[9] In the past, such *N*-glycosides have been considered to possess specific antiviral activity.[10] We used this method in attempts to prepare the 1-β-D-ribofuranoside of MBB, but always quantitatively recovered the MBB. This reduced reactivity of the NH group in HBB or in MBB might arise from steric or from bond-transmitted effects due to the 2 substituent. Ir and nmr spectra and ionization constants indicate that the latter effects are small.

Table I. Compounds Prepared by Direct 1-Alkylation



R	R¹	R²	R³	Mp, °C	Reactant	Yield, %	Yield, %[a]	Analyses
Pr	H	H	H	141-142	RI	50.5	51.8	
Bu	H	H	H	135-136	RI	68.5	39.7	
Benzyl	H	H	H	166-167	RBr	30.0	16.7	
Pr	Cl	H	H	172	RI	27.8	12.6	
Pr	H	Cl	H	143-144	RI	7.9[b]	–	C, H, Cl
Et	H	H	Me	Oil	RI	48.0[c]	45.4	
Allyl	H	H	H	144.5-145.5	RI	27.2[d]	–	C, H, N
Crotyl	H	H	H	155-156	RCl	19.6[e]	–	C, H, N

[a]Overall yield from the appropriate *o*-nitrochlorobenzene by previous method of D. G. O'Sullivan and A. K. Wallis [*Nature (London)*, 198, 1270 (1963)]. [b]White prisms from $MeNO_2$. [c]Purified *via* the picrate, mp 181-182°. [d]White prisms from aqueous MeOH. [e]White plates from EtOH.