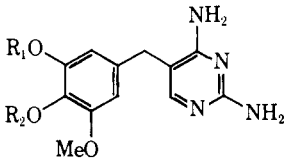
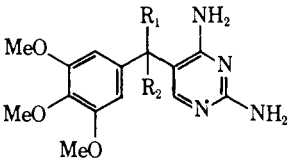
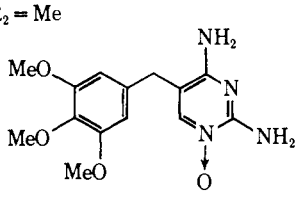


1, $R_1 = R_2 = Me$
2, $R_1 = Me$; $R_2 = H$
6, $R_1 = H$; $R_2 = Me$



3, $R_1 + R_2 = O$
4, $R_1 = H$; $R_2 = OH$



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Biological Results.[10]—Compound **4** was tested *in vitro* against various Gram-positive and Gram-negative bacteria and against three pathogenic fungi. Minimum inhibitory concentrations observed were 250 μg/ml against *Staphylococcus aureus* 209 and *Salmonella typhosa* F and 1000 μg/ml against *Escherichia coli* J and *Mycobacterium tuberculosis* H37Rv. The compound was inactive when tested against other representative Gram-positive and Gram-negative bacteria and against *Candida albicans*, *Trichophyton mentagrophytes*, and *Microsporum audouini*.

When tested *in vivo* against mice infected with *S. typhosa* P58a, **2** protected 50% of the animals at a dose of 206 mg/kg orally but was inactive at 1000 mg/kg against other representative bacterial infections. Compound **4** was without antibacterial activity when tested *in vivo* at 1000 mg/kg orally. No *in vivo* antifungal or antiviral activity was observed with either **2** or **4** nor was any antiprotozoal, anthelmintic, or antitumor activity observed with **4**.

When **2** and **4** were tested *in vivo* at a fixed concentration of 50 mg/kg orally in combination with graded doses of sulfisoxazole, **2** potentiated the activity of sulfisoxazole against infections with *E. coli* 257, *Staph. aureus* Smith, and *Proteus vulgaris* 190. No potentiation was observed when **2** was tested in combination with sulfisoxazole against other representative Gram-positive and Gram-negative bacteria. Compound **4** failed to exhibit a potentiative effect on the activity of sulfisoxazole against the organisms tested.

Experimental Section

2,4-Diamino-5-(3,5-dimethoxy-4-hydroxybenzyl)pyrimidine (2).—A mixture of 120 g (0.41 mole) of trimethoprim[1] (**1**) and 1 l. of 48% HBr was stirred at 95–100° for 100 min, the soln cooled, and 240 ml of 50% NaOH added. The acidic mixture was stored at room temp for 2 hr, the crystals filtered, washed with ice-water, dissolved in 500 ml of boiling H_2O, and neutralized with NH_4OH. The resulting crystals were filtered, washed (H_2O), and air-dried to give 84.5 g (75%) of **2**, mp 264–266°, identical (mmp, spectroscopic, and chromatographic properties) with an authentic sample.[9] *Anal.* ($C_{14}H_{16}N_4O_3$), C, H, N.

2,4-Diamino-5-(3,4,5-trimethoxybenzoyl)pyrimidine (3).—A mixture of 50 g (0.17 mole) of **1** and 56 g of MnO_2 in 1 l. of 99% HOAc was stirred and refluxed for 4 hr and then stored at room temp overnight and the crystalline $Mn(OAc)_2$ filtered and washed with 150 ml of HOAc. The combined filtrates were rendered strongly acidic with 35–40 ml of concd HCl and evapd, the residua hydrochloride was slurried with H_2O, filtered, dissolved in hot H_2O, and neutralized with NH_4OH. The resulting ppt was collected and crystd from 65% EtOH to give 29 g (56%) of **3**, mp 198–199°. *Anal.* ($C_{14}H_{16}N_4O_4$), C, H, N.

Racemic α-(2,4-Diamino-5-pyrimidyl)-3,4,5-trimethoxybenzyl Alcohol (4).—To a stirred and refluxing soln of 12.5 g (0.04 mole) of **3** in 250 ml of MeOH was added 3 g of $NaBH_4$ over 1 hr. The mixture was stirred an additional hr and evapd and the residue crystd first from H_2O and then from EtOH to give 11.3 g (90%) of **4**, mp 199–200°, identical (mmp, spectroscopy, and chromatography) with metabolite M_2.[11]

(10) For *in vitro* and *in vivo* test methodologies, see E. Grunberg, J. Berger, G. Beskid, R. Cleeland, H. N. Prince, and E. Titsworth, *Chemotherapia*, **12**, 272 (1967), and ref 3.

(11) We are indebted to our colleagues Drs. R. Reiner and G. Rey-Bellet Chemical Research Department, F. Hoffmann-La Roche & Co., A. G., Base for this comparison.

Preparation and Antimicrobial Activity of *N*-Thiadiazolylcarbamic Acid Esters

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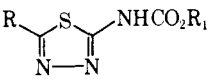
Received July 14, 1970

Recently we reported the adverse effect of *N*-thiadiazolylcarbamic acid *n*-butyl ester on measles virus in Vero cells.[1] In continuation of our search for potent antiviral and antimicrobial agents in 1,3,4-thiadiazolyl series,[1,2] compounds listed in Table I were prepared by interaction of alkyl chloroformates with appropriate 3-aminothiadiazoles (eq I).

TABLE I

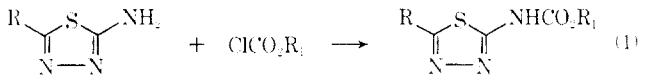


No.	R	R_1	Yield, %	Mp, °C	Formula[a]
1	H	CH_3	68	230	$C_4H_5N_3O_2S$
2	H	C_2H_5	73	206	$C_5H_7N_3O_2S$
3	H	*i*-C_3H_7	71	191	$C_6H_9N_3O_2S$
4	H	*n*-C_4H_9	83	110	$C_7H_{11}N_3O_2S$
5	H	*i*-C_4H_9	89	147	$C_7H_{11}N_3O_2S$
6	H	$CH_2C_6H_5$	69	146	$C_{10}H_9N_3O_2S$
7	CH_3	CH_3	86	215	$C_5H_7N_3O_2S$
8	CH_3	C_2H_5	78	177	$C_6H_9N_3O_2S$
9	CH_3	*i*-C_3H_7	90	164	$C_7H_{11}N_3O_2S$
10	CH_3	*n*-C_4H_9	75	142	$C_8H_{13}N_3O_2S$
11	CH_3	*i*-C_4H_9	84	140	$C_8H_{13}N_3O_2S$
12	CH_3	$CH_2C_6H_5$	82	205	$C_{11}H_{11}N_3O_2S$
13	C_2H_5	CH_3	73	175	$C_6H_9N_3O_2S$
14	C_2H_5	C_2H_5	66	145	$C_7H_{11}N_3O_2S$
15	C_2H_5	*i*-C_3H_7	74	140	$C_8H_{13}N_3O_2S$
16	C_2H_5	*n*-C_4H_9	69	130	$C_9H_{15}N_3O_2S$
17	C_2H_5	*i*-C_4H_9	82	150	$C_9H_{15}N_3O_2S$
18	C_2H_5	$CH_2C_6H_5$	71	180	$C_{12}H_{13}N_3O_2S$
19	CF_3	CH_3	86	196	$C_5H_4F_3N_3O_2S$
20	CF_3	C_2H_5	91	183	$C_6H_6F_3N_3O_2S$
21	CF_3	*i*-C_3H_7	88	144	$C_7H_8F_3N_3O_2S$
22	CF_3	*n*-C_4H_9	90	158	$C_8H_{10}F_3N_3O_2S$
23	CF_3	*i*-C_4H_9	92	150	$C_8H_{10}F_3N_3O_2S$
24	CF_3	$CH_2C_6H_5$	89	180	$C_{11}H_8F_3N_3O_2S$

[a] All compounds were analyzed for C, H, and the analytical results were satisfactory. Ir and nmr spectra were as expected.

(1) H. Mirshamsi, I. Lalezari, M. Kamali, G. Niloufari, and N. Rezvani, *Arch. Virusforsch.*, **29**, 267 (1970).

(2) I. Lalezari and N. Sharghi, *J. Heterocycl. Chem.*, **3**, 336 (1966).



Antimicrobial Activity.—The compounds listed in Table I were tested *in vitro* against *Escherichia coli*, *Bacillus anthracis*, and *Staphylococcus aureus*, using a tube dilution method and the disk diffusion method.[3] Of all the compounds tested, *N*-[5-trifluoromethyl-1,3,-4-thiadiazol-2-yl]carbamic acid *n*-butyl ester (**22**) at 200 μg/ml inhibited the growth of *B. anthracis*, after 24 hr incubation at 37°. All other compounds showed only slight antimicrobial activity probably due to low solubility and/or poor diffusion.

Experimental Section[4]

***N*-[5-Trifluoromethyl-1,3,4-thiadiazol-2-yl]carbamic Acid *n*-Butyl Ester (22).**—2-Amino-5-trifluoromethyl-1,3,4-thiadiazole[2] (1.67 g, 0.01 mole) in 15 ml of dry $CHCl_3$, was refluxed for 5 hr with 1.64 g (0.012 mole) of *n*-butyl chloroformate. Removing the solvent followed by crystn of the residue from 50% aq EtOH, gave 2.42 g (90%) of **22**, white crystals, mp 158°. The other compds listed in Table I were prepared similarly.

Acknowledgments—The authors gratefully acknowledge the constant encouragement of Dr. A. Alikhani of Tehran University.

(3) C. H. Collins, "Microbiological Methods," Butherworths, London (1964).

(4) Melting points were taken on a Kofler hot stage microscope and were uncorrected. The ir spectra were determined with a Leitz Model III spectrograph. Nmr spectra were obtained on a Varian A60A instrument.

A New Series of Antiarrhythmic Agents. The 2-Aminotetralins[1a]

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Received May 16, 1970

The synthesis and analgetic properties of some substituted 2-aminotetralins were previously reported by Martin, *et al.*[2] Subsequent pharmacological investigations have shown these compounds to possess marked negative chronotropic and mild negative inotropic activities in spontaneously beating guinea pig atria.[3] In order to determine the relationship between the toxicity and the antifibrillatory activity of the series of 2-aminotetralins *in vivo* a screening method developed by Lawson[4] was used. This procedure enables rapid screening of the compounds with a large number of mice and a relatively small quantity of drug. The mice are pretreated with the test compounds at a set period before induction of arrhythmias with $CHCl_3$. During this period symptoms of acute toxicity (ataxia, convulsions, etc.) can be noted. The mouse is then subjected to a $CHCl_3$ atmosphere until respiration ceases. This procedure induces a high incidence of ventricular fibrillation in the animals. In the exposed hearts the fibrillatory movements can be observed and the cardiac rate counted. The protection afforded by pretreatment with an antiarrhythmic compound can then be determined.

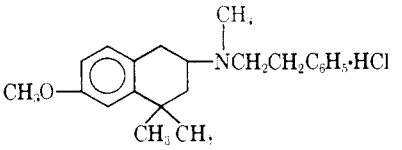
Results and Discussion

N-Methyl-*N*-phenylethyl-1,2,3,4-tetrahydro-6-methoxy-4,4-dimethyl-2-naphthylamine hydrochloride (1) had previously been shown to possess potent myocardial depressant activity.[2] Because of its past indications of antiarrhythmic activity and because of its availability **1** was investigated in detail. The results are shown in Table I. The procedure used to induce

TABLE I
CHLOROFORM-INDUCED CARDIAC ARRHYTHMIAS BEFORE AND AFTER TREATMENT WITH **1**

Dose (mg/kg)	Number of mice	% protected	Average rate (beats/min ± S.E.)	% toxic	% fatal
Controls	40	0.3	351.91 ± 16.61	0.0	0.0
50	40	5.0	289.62 ± 10.63	0.0	0.0
75	40	32.5	228.00 ± 14.83	0.0	0.0
100	40	55.0	166.08 ± 13.19	0.0	0.0
125	40	72.5	146.88 ± 13.04	15.0	0.0
150	40	92.5	136.09 ± 7.74	47.5	0.0
175	40	100.0	124.24 ± 6.75	69.4	7.5

arrhythmias *in vivo* resulted in the production of arrhythmia and fibrillation in 100% of the nontreated control animals. The ED_{50} of **1** was 94.41 mg/kg



1

(0.262 mmole/kg). The average heart rate corresponding to this dose was graphically estimated to be 160 beats/min. No toxicity was noted at this ED_{50} dose. Compound **1** showed a good degree of antiarrhythmic activity in relation to its toxicity. Only at the higher doses, approaching 100% protection, does significant toxicity result, generally manifested as mild ataxia. Convulsions and death occurred only at the highest dose studied. This compound was used as a standard for comparison of all the other analogs tested. The doses used for the other compounds were the equimolar equivalents of the ED_{50} dose for **1** (0.262 mmole/kg). The results are shown in Table II. The analogs **2–5** have chemical structures most closely resembling **1**. These compounds involve only substitutional changes on N atom. They varied greatly in activity ranging from 0 to 100% protection from fibrillation. The

* To whom correspondence concerning this research should be addressed.

(1) (a) This research was supported in part by a Washington State Heart Association Grant No. 6970-6. (b) National Science Foundation Fellow, 1969–1970.

(2) A. R. Martin, A. P. Parulkar, D. J. Gusseck, L. J. Anderson, G. L. Grunewald, and A. I. White, *J. Pharm. Sci.*, **58**, 340 (1969). (b) V. S. Pai, A. P. Parulkar, A. R. Martin, and A. I. White, *ibid.*, in press.

(3) W. E. Johnson, D. M. Graeff, A. R. Martin, and A. I. White, *Life Sci.*, **9**, 471 (1970).

(4) J. W. Lawson, *J. Pharmacol. Exp. Ther.*, **160**, 22 (1968).