ml of CF_3COOH and stirred at 0° for 3 hr. The CF_3COOH was removed *in vacuo* to yield a yellow oil which was then dissolved in slightly basic aq soln. The aq phase was extd several times with $CHCl_3$ to remove any unreacted starting material. The aq soln was made slightly acidic and the org acid which pptd was removed by filtration and dried to give 0.90 g (81% yield) of white solid. Recrystn from PhH–Me_2CO gave 0.86 g of product; mp 180.0–180.5°. *Anal.* ($C_{19}H_8N_8O_4$) H, N; Calcd C, 67.45; found, 68.08.

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Synthetic Biologically Active Polymers. 7. Antibacterial Activity of Some Sulfonamide–Formaldehyde Copolymers

L. GUY DONARUMA* AND JOHN RAZZANO[1]

Department of Chemistry, Institute of Colloid and Surface Science, Clarkson College of Technology, Potsdam, New York 13676

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Chemistry.—In previous publications[2] we have described the preparation and certain biological activities of a number of synthetic biologically active polymers. Activities dealing with antimalarial properties of some sulfonamide–formaldehyde copolymers were among these reports.[2c-e] Since these latter reports, we have begun to screen the same or analogous copolymers more broadly. This report concerns the antibacterial activity of three sulfonamide–formaldehyde copolymers (see Table I) and a sulfone–formaldehyde copolymer. The copolymers were prepared by methods reported earlier.[2c-e]

Biological Activity.—As can be seen from Table I, in most tests, the monomer and the polymer had approximately equivalent antibacterial activity under the test conditions employed with a general tendency for the monomer activity to be higher. Thus, it continues to appear that polymerization of drugs may be useful as a method to prepare novel drug systems.

Employing three samples of the 4,4′-diaminodiphenylsulfone–formaldehyde copolymer of differing molecular weights[2e] in the antibacterial testing gave results (see Table I) which indicated that in this copolymer system, only a very minor indication of variation of activity with molecular weight was observed.

Experimental Section

All formaldehyde copolymers were prepared and characterized as reported earlier.[2c-e]

Antibacterial screening was carried out by seeding Mueller-Hinton agar with the test organisms and adding antibiotic assay cylinders to each petri dish. Each compound tested was added to the cylinders as a 1% solution in DMF. Each monomeric sulfonamide drug and the corresponding formaldehyde copolymer were tested at the same time. After overnight incubation at 37°, the zones of inhibition were measured. They were generally of the order of magnitude of 20–30 mm, even though the total lowest value observed was 10 mm and the highest 35 mm.

TABLE I

RELATIVE ANTIBACTERIAL ACTIVITY OF SOME SULFONAMIDE DRUGS (M) AND THE FORMALDEHYDE COPOLYMERS (P) THEREOF

Sulfonamide system	Test organism	Relative activity M	P	
Sulfapyridine	*Staphylococcus pyogenes*	1.1	1.0	
	Escherichia coli	1.7	1.0	
	Aerobacter aerogenes	1.1	1.0	
	Pseudomonas aeruginosa	1.1	1.0	
Sulfabenzamide	*Staph. pyogenes*	1.5	1.0	
	E. coli	1.0	1.0	
	A. aerogenes	1.4	1.0	
Sulfanilamide	*Staph. pyogenes*	1.2	1.0	
	E. coli	1.2	1.0	
	A. aerogenes	1.1	1.0	
	Ps. aeruginosa	1.8	1.0	
4,4′-Diaminodiphenylsulfone	*Staph. pyogenes*	1.4	1.0	($\bar{m}_w$ = 4700)[a]
		1.7	1.0	($\bar{m}_w$ = 7600)
		1.3	1.0	($\bar{m}_w$ = 10,000)

[a] $\bar{m}_w$ = weight average molecular weight ± 10%.[2e]

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New Thiocarboxamides Derivatives with Specific Gastric Antisecretory Properties

CHARLES E. MALEN, BERNARD H. DANREE,

Chemical Research Division,

AND XAVIER B. L. PASCAUD*

Pharmacological Research Division, Science Union et Associés Groupe de Recherches des Laboratoires Servier-92-Suresnes, France

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Atropine-like drugs with their troublesome systemic side effects were, for a long time, the only products available for gastric antisecretory properties in ulcer therapy. During the past few years attempts have been made to find specific gastric antisecretory products acting by a nonanticholinergic pathway.

A well-documented review has just been published on this subject.[1] Among newly described chemicals, the most studied, 2-phenyl-2-(2-pyridyl)thioacetamide (PPT),[2] although not possessing really specific antigastrin properties,[3] seems to be the most available. Surprisingly, very few derivatives of this structure have been described. In the course of a research program on antiulcer compounds, we therefore synthesized some thiocarboxamides. Although completely devoid of anticholinergic activity, most of these compounds pos-

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TABLE I
$R_1R_2CHCSNH_2$

No.	R_1	R_2	Mp, °C	Crystallization Solvent	Formula	Corresponding nitrile: Bp, °C (mm) or mp, °C	Corresponding nitrile: $nD^{t°}$
1	H	2-Py	190–192[a]	MeOH	$C_7H_8N_2S \cdot HCl$	65–70 (0.05)[e]	1.5262 (23)
1a	H	2-Py	90–92[a]	H_2O	$C_7H_8N_2S$		
2	CH_3	2-Py	163–164	ACOEt	$C_8H_{10}N_2S \cdot HCl$	50–54 (0.05)[f]	1.5072 (26)
2a	CH_3	2-Py	112–113	C_6H_6–cyclohexane	$C_8H_{10}N_2S$		
3	C_2H_5	2-Py	180–181	ACOEt–EtOH	$C_9H_{12}N_2S \cdot HCl$	60–65 (0.1)[g]	1.5058 (22)
3a	C_2H_5	2-Py	108–109	C_6H_6	$C_9H_{12}N_2S$		
4	$CH_3(CH_2)_2$	2-Py	160–162	EtOH	$C_{10}H_{14}N_2S \cdot HCl$	68–70 (0.1)[g]	1.5037 (23)
4a	$CH_3(CH_2)_2$	2-Py	93–94	Cyclohexane	$C_{10}H_{14}N_2S$		
5	$(CH_3)_2CH$	2-Py	198–200	EtOH–cyclohexane	$C_{10}H_{14}N_2S \cdot HCl$	48–52 (0.01)	1.5028 (22)
5a	$(CH_3)_2CH$	2-Py	163–164	ACOEt	$C_{10}H_{14}N_2S$		
6	$CH_3(CH_2)_3$	2-Py	159–160	EtOH	$C_{11}H_{16}N_2S \cdot HCl$	76–80 (0.04)[g]	1.5008 (20)
6a	$CH_3(CH_2)_3$	2-Py	104–105	Cyclohexane	$C_{11}H_{16}N_2S$		
7	$(CH_3)_2CHCH_2$	2-Py	138–140	C_6H_6–cyclohexane	$C_{11}H_{16}N_2S$	76–80 (0.1)[g]	1.4982 (22)
8	$CH_3(CH_2)_5$	2-Py	75–76	Cyclohexane	$C_{13}H_{20}N_2S$	97–100 (0.04)[g]	1.4971 (19)
9	$CH_2{=}CHCH_2$	2-Py	140–141	ACOEt–EtOH	$C_{10}H_{12}N_2S \cdot HCl$	72–74 (0.3)[f]	1.5175 (24)
9a	$CH_2{=}CHCH_2$	2-Py	74–75	Cyclohexane	$C_{10}H_{12}N_2S$		
10	2-Py	2-Py	195	MeOH	$C_{12}H_{11}N_3S \cdot 2HCl$	139–140[h]	
10a	2-Py	2-Py	161–162	EtOH	$C_{12}H_{11}N_3S$		
11	2-Pyrazinyl	2-Py	214–215	Sublimation	$C_{11}H_{10}N_4S$	193–194	
12	H	2-Pyrazinyl	113–114	C_6H_6	$C_6H_7N_3S$	80–87 (0.1);[i] mp 33–34°	
13	C_2H_5	2-Pyrazinyl	88–90	C_6H_6	$C_8H_{11}N_3S$	72–74 (0.06)[i]	1.5142 (24)
14	C_6H_5	2-Pyrazinyl	142–143	MeCN	$C_{12}H_{11}N_3S$	133–134[i]	
15	C_6H_5	2-Pyrimidyl	185–186	MeCN	$C_{12}H_{11}N_3S$	132–140 (0.03);[j] mp 64–65°	
16	4 Cl-C_6H_4	2-Pyrimidyl	155–158	EtOH–H_2O	$C_{12}H_{10}ClN_3S$	150–160 (0.2); mp 71–73°	
17	H	2-(4,6-Me_2)-pyrimidyl	149–150	EtOH	$C_8H_{11}N_3S$	80–81	
18	H	4(5)-Imidazolyl	183–184	EtOH	$C_5H_7N_3S$	138–139[k]	
19	C_6H_5	2-Thiazolyl	125–126	EtOH	$C_{11}H_{10}N_2S$	115–125 (0.01);[l] mp 42–44°	
20	C_6H_5	C_6H_5	152–153[b]	MeOH	$C_{14}H_{13}NS$		
21	2-$PyCH_2$	H	196–198	EtOH	$C_8H_{10}N_2S \cdot HCl$	80–85 (0.1)[m]	1.5211 (23)
21a	2-$PyCH_2$	H	139–140	EtOH	$C_8H_{10}N_2S$		
22	$HN{=}CCH_3$	H	140–141[c]	C_6H_6	$C_4H_8N_2S$		
23	2-Py	Acetamide	123–124[d]		$C_7H_8N_2S$		

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sess specific and powerful gastric antisecretory properties.

In this note, we report the synthesis, preliminary pharmacological results, and a first approach to structure–activity relationships of 22 thiocarboxamides. A few of these were selected for a more complete pharmacological study which will be published in detail later.

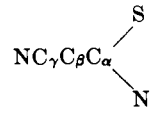
Chemistry.—All thiocarboxamides synthesized are listed in Table I. The derivatives with sufficiently basic properties to give nonhydrolyzable salts in aq soln were studied as hydrochlorides.

The thiocarboxamides were synthesized from the corresponding nitriles by reaction with H_2S in pyridine–Et_3N at ordinary temp or in sealed tubes at 100°.[4]

The nitriles were synthesized by known procedures (*cf.* Table I). Purity was determined by potentiometric titration in AcOH and, if possible, by glc (SE_{30} 5% on Aeropak or CAR 20 M 5% on Chromosorb).

Structure–Activity Relationship.—Compounds **1**, **2**, **4**, **5**, **6**, **8**, **9**, **13**, **14**, and **16** are more active than PPT, an agent fully described.[2] Based on their therapeutic index* the activity of **1**, **5**, and **16** is about the same as that of atropine ip.

In a first approach to a structure–activity relationship, it seems that the antisecretory activity is related to the grouping



The following substitutions have been made, and either lower the activity very much, or completely suppress it: (a) the substitution of S by O (**23**); (b) two instead of one NC chain in the γ position to the thiocarboxamide group (**10**, **11**); (c) no N in the side chain (**20** and thioacetamide); (d) lengthening of the distance between the nonamide N and the thiocarboxamide group (**21**). N in the γ position to the thiocarboxamide group seems to be necessary for the activity, and it may or may not be implicated in a ring (**22**). However, two compounds with a pentacyclic ring, though having N in

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* Therapeutic Index = ED_{50} /LD_{50} (Shay rat). Atropine sulfate = 448; **1** = 404; **5** ≥ 526; **16** ≥ 667; PPT, HCl = 222.

TABLE II

No.	Toxicity LD_{50}, mg/kg per os (mice)	Gastric antisecretory activity ED_{50}, mg/kg Shay rat[b]	Anticholinergic activity pA_2[c]
1	570[d] (545–595)	1.42	$>10^{-4}$
2	618 (573–668)	2.30	$3.5 \cdot 10^{-5}$
3	673 (576–787)	5.10	$>10^{-4}$
4	628 (576–686)	4.05	$>10^{-4}$
5	>1.000	1.90	$1.25 \cdot 10^{-4}$
6	470 (398–554)	2.64	$>10^{-4}$
7	>1.000	11.50	$>10^{-4}$
8	>1.000	3.70	$>10^{-4}$
9	575 (532–623)	3.25	$>10^{-4}$
10	70 (58.6–83.6)	NA (20)	
11	>1.000	NA (100)	
12	>1.000	16.2	$>10^{-4}$
13	830 (686–1004)	4.28	$>10^{-4}$
14	924 (775–1101)	4.32	$>10^{-4}$
15	>1.000	7.90	$>10^{-4}$
16	>1.000	1.50	$>10^{-4}$
17	>1.000	7.82	$>10^{-4}$
18	>1.000	NA (100)	
19	>1.000	50	$>10^{-4}$
20	>1.000	82	
21	653 (568–751)	NA (50)	$>10^{-4}$
22	>1.000	4.60	$>10^{-4}$
23	>1.000	NA (100)	$>10^{-4}$

Reference products	LD_{50}[a]	ED_{50} Shay-rat	pA_2[c]
Atropine sulfate[e]	207 ip (182–227)	0.462 ip	$1.6 \cdot 10^{-8}$
PPT·HCl[f]	592 po (526–667)	5.40[b]	$>10^{-4}$
Thioacetamide[g]	≃220 ip	35.0 ip	

[a] Acute toxicity was determined orally in male albino mice CD strain. LD_{50} calcd by C. S. Weil's method [*Biometrics*, **8**, 249 (1962)]. Numbers in parentheses are fiduciary limits of LD_{50}. [b] Compounds are given by intraduodenal route. NA = inactive compound. Numbers in parentheses are the maximum dose assayed. [c] Anticholinergic activity was established on perfused guinea pig ileum by pA_2 technique [E. Bulbring, A. Grema, and O. R. Saxby, *Brit. J. Pharmacol.*, **13**, 440 (1958)]. Drugs were dissolved in 0.9% saline. [d] Van Tamelen and Baran (footnote *a*, Table I) have LD_{50} mice as 750 mg/kg sc. [e] Atropine sulfate from FLUKA AG, Buchs (Switzerland). [f] 2-Phenyl-2-(2-pyridyl)thioacetamide·HCl synthesized in our laboratories. [g] Thioacetamide from Schuchardt, München (Germany).

this position, were inactive (**18**) or showed only mild activity (**19**).

Experimental Section

2-(2-Pyridyl)butanothioamide (5a).—2-(2-Pyridyl)butanonitrile (8.2 g, 0.056 mole) was dissolved into a mixture of Et_3N (5.6 g, 0.056 mole) and pyridine (8 g). The soln was satd with dry H_2S at room temp and treated in a sealed tube to 100° and maintained for 15 hr. After cooling, the mixture was poured into H_2O (100 ml). The suspension was extracted with $CHCl_3$, the extracts were washed (H_2O), dried (Na_2SO_4), and concd under vacuum. The solid residue was recrystd from C_6H_6 to give 6 g (60%), mp 108–109°. *Anal.* ($C_9H_{12}NS$) N, S.

The hydrochloride was prepared by adding etheral 4 *N* HCl (6 ml) to **3a** (4 g) in EtOH (150 ml). The solvents were removed under vacuum and the residue was recrystd from 90 ml of EtOAc–EtOH (50:40); yield 3.9 g (80%), mp 180–181° dec. *Anal.* ($C_9H_{12}NS \cdot HCl$) N, S.

Gastric Antisecretory Activity in the Rat.—Gastric antisecretory activity was evaluated in the 4 hr polyrus-ligated rat, using the technique of Shay.[5] The compds were suspended in 20% gum syrup, and were administered intraduodenally immediately after pyloric ligation to groups of 6 male Sprague Dawley/CD rats weighing 221 ± 1.77 g.† Free acid output was calcd for each rat and expressed as μequiv/4 hr per 100 g of body weight. Data of the whole test series have been pooled for the control group (185 rats),‡ and the mean value of each group receiving drugs was compared to the mean value of this control group using the Student's "*t*" test. Per cent inhibition was calcd in comparison with the control values representing 100%, and plotted on semilogarithmic paper *vs.* mg/kg of dose. ED_{50} was read from the graph. Three to five doses were used for each compound.

After completion of this manuscript, some pharmacological results on 2-pyridyl thioacetamide were described by J. Borsy, *et al.*, at the 4th World Congress of Gastroenterology in Copenhagen. These results are in full agreement with ours.

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† $m \pm$ standard error of the mean.

‡ Control values for these experiments with 185 rats were: vol: 3.09 ± 0.06 ml/4 hr per 100 g. Free acid concn: 85.8 ± 1.2 mequiv/l. Free acid output: 271.8 ± 7.9 μequiv/4 hr per 100 g. Total acid concn: 111.0 ± 1.0 mequiv/l. Total acid output: 348 ± 8.6 μequiv/4 hr per 100 g.

Antimicrobial Compounds. 1. Synthesis and Antimicrobial Activity of Some Alkylidene, Cycloalkylidene, and Arylidene Derivatives of 3-Hydrazinopyridazine

M. LIKAR, B. DRINOVEC,

Institute of Microbiology, University of Ljubljana, Ljubljana, Yugoslavia

M. JAPELJ,* A. POLLAK, A. POVŠE, AND P. JERMAN

Research and Development Institute, Krka, Pharmaceutical and Chemical Works, Novo Mesto, Yugoslavia

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Various sulfonamidopyridazines[1,2] have been reported to have antibacterial activity with a low toxicity. In our experiments we have found that 3-thenoylamino-6-chloropyridazine[3] exhibits good antimicrobial activity. A number of hydrazinopyridazines[4] and a few alkylidenehydrazinopyridazines[5] have been reported to

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