TABLE V
ORAL DIURETIC ACTIVITY IN DOGS

No.	Dose, mg/kg	Collection period, hr	Urine[a] volume	Ions excreted[a] Na^+	K^+	Cl^-
2a	10	0–6	246	16.1	8.9	6.2
		0–24	346	26.1	21.0	11.4
2b	10	0–6	251	8.2	3.7	2.1
		0–24	308	8.9	6.4	3.0
2c	10	0–6	303	11.0	4.2	2.8
		0–24	364	12.2	7.6	7.2
2e	10	0–6	382	13.4	8.3	7.7
		0–24	422	13.8	12.4	8.6
3b	10	0–6	270	8.1	3.6	2.5
		0–24	330	9.2	6.1	4.2
5	5	0–6	338	9.3	4.7	4.9
		0–24	408	11.5	9.7	8.3

[a] Per cent increase over that produced by starch.

In rat studies the derivatives produced 5-hr and 24-hr urine volumes comparable to those of the parent sulfonamides, and several were more efficient as stimulants of Cl^- excretion. In dogs, the urinary electrolyte patterns produced by the aminomethyl derivatives resembled those of the parents, *i.e.*, the new compounds appear to be carbonic anhydrase inhibitors (Table V). In addition, the urine flow in all cases was comparable with that produced by **2a**. Quantitatively, the excretion of Na^+, K^+, and Cl^- stimulated by the test compounds in dogs was somewhat lower than that produced by **2a**. The similarity in the activities of all of the derivatives and the parent compounds in rats and dogs supports the hypothesis that the derivatives are readily hydrolyzed *in vivo* to the parent sulfonamides, as does their instability during the attempted pK_a measurements.

Experimental Section

5-Acetamido-*N*-piperidinomethyl-1,3,4-thiadiazole-2-sulfonamide (2b).—To a soln of 5.5 g (0.025 mole) of 5-acetamido-1,3,4-thiadiazole-2-sulfonamide (**2a**) and 5 ml (4.31 g, 0.05 mole) of piperidine in 50 ml of MeOH was added 5 ml (0.067 mole) of 37% CH_2O. The reaction mixt was kept at room temp overnight, and the product was collected by filtration and dried *in vacuo* at 60°. Compounds **2c-i**, **3b-c**, and **4b** were also made by this procedure; when the product did not crystallize spontaneously, the soln was coned as needed. For **2g** the initial pH was adjusted to 7.5.[8]

***N,N'*-Methylenebis(5-acetamido-1,3,4-thiadiazole-2-sulfonamide) (5).**—A suspension of **2a** (5.5 g, 0.025 mole) in 50 ml of MeOH was heated on a steam bath. After 2 min 37% CH_2O (5.0 ml, 0.067 mole) was added, and the mixt was heated for 30 min, allowed to cool for 1 hr, and filtered. The product was washed with MeOH and dried *in vacuo*. The yield was 4.0 g (72%).

2c·HCl.—Dry HCl was bubbled for 5 min through a soln of 1.8 g of **2c** in 10 ml of Et_2O and 30 ml of Me_2CO. After 30 min the product was collected and dried *in vacuo*. The yield was 1.3 g (65%).

5-Acetamido-*N*-acetyl-1,3,4-thiadiazole-2-sulfonamide (4a).—A mixt of 5 g of **2a**, 25 g of anhyd NaOAc, and 35 ml of Ac_2O was heated on a steam bath for 1 hr and poured into 300 ml of ice water. The resulting mixt was kept at 4° overnight and filtered. The solid was resuspended in H_2O, filtered, washed (H_2O), and dried to give 4.1 g of crude product. Recrystn from EtOH gave 3.75 g (63%) of **4a**.

Solubility Studies.—To determine the H_2O solubilities the solute content of a measured vol of filtered, satd soln was ascertained by evapn and weighing. To determine the propylene glycol solubilities, a nearly satd soln was prepd at 60–70° from a weighed sample of compound and kept at room temp overnight. The solid material which sepd on standing was filtered, dried, and weighed.

(8) See ref 3c for specific procedures for several of these compounds.

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Synthetic Biologically Active Polymers. 8. Antibacterial Activity of Some Sulfonamide–Dimethylolurea Copolymers

JOHN R. DOMBROSKI[1] AND L. GUY DONARUMA*

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

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Chemistry.—Previous publications in this series have described the synthesis, characterization, and certain biological activities of a number of polymers and copolymers.[2] Papers 3–7 deal with formaldehyde copolymers of sulfonamide drugs.[2c-f] This publication will describe the antibacterial activity of a second type of sulfonamide copolymer, namely, sulfonamide–dimethylolurea copolymers. These polymers were prepared so that the biological effect of employing a comonomer other than formaldehyde with the sulfonamides might be observed. The sulfonamide–dimethylolurea condensates were prepared and characterized as reported previously.[2g]

Biological Activity.—Table I displays information concerning the antibacterial activity of certain sulfonamides and sulfone vinylogs and their respective dimethylolurea copolymers. As can be seen, the antibacterial activities of the sulfonamides (M) and the copolymers (P) do not really differ appreciably. Thus, in general, while all three logical occurrences which might be expected to be observed relative to the antibacterial activity of the sulfonamides upon incorporation into the copolymer (antibacterial activity: (1) stays the same, (2) increases, (3) decreases) can be observed, the differences are very small. However, this is relatively interesting because even though the sulfonamide content of the copolymers (P) is smaller than that in equivalent test dosages of the sulfonamide monomers (M), the antibacterial activity did not drop markedly in the copolymers (P). This same phenomenon was observed in the case of antibacterial activity in the sulfonamide drugs relative to the CH_2O copolymers of the same

(1) Taken in part from the thesis submitted by Mr. John R. Dombroski in partial fulfillment of the requirements for the Master of Science degree.

(2) (a) R. J. Cornell and L. G. Donaruma, *J. Polym. Sci.*, **3A**, 827 (1965). (b) R. J. Cornell and L. G. Donaruma, *J. Med. Chem.*, **8**, 388 (1965). (c) L. G. Donaruma and J. Razzano, *ibid.*, **9**, 258 (1966). (d) J. R. Dombroski, L. G. Donaruma, and J. Razzano, *ibid.*, **10**, 963 (1967). (e) J. R. Dombroski, L. G. Donaruma, and J. Razzano, *ibid.*, **10**, 964 (1967). (f) Paper 7 of this series: L. G. Donaruma and J. Razzano, *ibid.*, **14**, 244 (1971). (g) J. R. Dombroski, "The Condensation of Some Sulfonamides with Dimethylolurea," M.S. Thesis, Clarkson College of Technology, Oct 9, 1967. Paper 6 of this series: J. R. Dombroski and L. G. Donaruma, submitted for publication.

CHART I

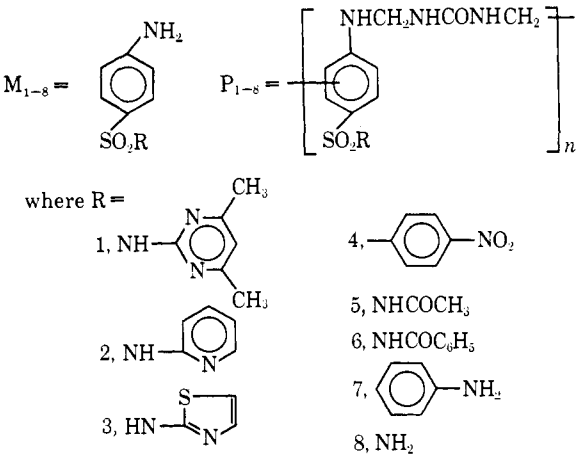


TABLE I

ANTIBACTERIAL ACTIVITY OF SOME SULFONAMIDE DRUGS (M) AND THE CORRESPONDING DIMETHYLOLUREA COPOLYMERS (P)[a-c]

Sulfonamide system	Test organism[d]	Relative activity M	Relative activity P
Sulfamethazine (M_1, P_1)	1	1.1	1.0
	2	1.1	1.0
	3	1.0	1.2
	4	1.1	1.0
Sulfapyridine (M_2, P_2)	1	1.0	1.3
	2	1.1	1.0
	3	1.0	1.1
	4	1.0	1.0
Sulfathiazole (M_3, P_3)	1	1.0	1.0
	2	1.1	1.0
	3	1.2	1.0
	4	1.1	1.0
4-Nitro-4′-aminodiphenylsulfone (M_4, P_4)	1	1.0	1.2
	2	1.0	1.1
	3	1.0	1.0
	4	1.0	1.0
Sulfacetamide (M_5, P_5)	1	1.1	1.0
	2	1.3	1.0
	3	1.3	1.0
	4	1.0	1.0
Sulfabenzamide (M_6, P_6)	1	1.0	1.1
	2	1.0	1.1
	3	1.2	1.0
	4	1.0	1.1
4,4′-Diaminodiphenylsulfone (M_7, P_7)	1	1.2	1.0
	2	1.1	1.0
	3	1.0	1.1
	4	1.1	1.0
Sulfanilamide (M_8, P_8)	1	1.0	1.1
	2	1.1	1.0
	3	1.0	1.0
	4	1.2	1.0

[a] Structures for M and P are as in Chart I. [b] All copolymers were prepd and characterized as reported in other publications.[2c-g] [c] Antibacterial testing was carried out by seeding Mueller-Hinton agar with the test organisms and adding antibiotic assay cylinders to each petri dish. To the cylinders, each compd tested was added as a 1% soln in DMF. Each monomeric sulfonamide drug (M_{1-8}) and the corresponding dimethylolurea copolymers (P_{1-8}) were tested at the same time. After overnight incubation at 37°, the zones of inhibition were measured. The zones of inhibition were generally of the order of 20–30 mm even though the lowest measured value was 10 mm and the highest 37 mm. [d] Test organisms: (1) *Staphylococcus pyogenes;* (2) *Escherichia coli;* (3) *Aerobacter aerogenes;* (4) *Pseudomonas aeruginosa.*

drugs.[2f] This suggests that the antibacterial activity observed for the copolymers is not related *only* to the sulfonamide content of the copolymers.

Another interesting comparison can be obtained if the relative antibacterial activities of the sulfonamide–CH_2O copolymers (F) and the sulfonamide–dimethylolurea copolymers (D) are calcd for the comparative data available.[2f] Table II displays these results.

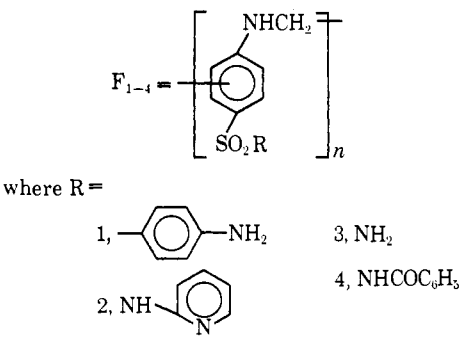
TABLE II

SOME RELATIVE ANTIBACTERIAL ACTIVITIES OF A SERIES OF SULFONAMIDE–FORMALDEHYDE COPOLYMERS (F) AND A SERIES OF SULFONAMIDE–DIMETHYLOLUREA COPOLYMERS (D)[a-c]

Sulfonamide system	Test organism[d]	Relative activity F	Relative activity D
4,4′-Diaminodiphenyl sulfone (F_1, D_1)	1	1.0	1.0
Sulfapyridine (F_2, D_2)	1	1.0	1.4
	2	1.0	1.2
	3	1.0	1.5
	4	1.0	1.0
Sulfanilamide (F_3, D_3)	1	1.4	1.0
	2	1.2	1.0
	3	1.2	1.0
	4	1.0	1.9
Sulfabenzamide (F_4, D_4)	1	1.0	2.3
	2	1.0	3.2
	3	1.0	2.6

[a] The CH_2O copolymers (F) of the sulfonamide drugs have the structures shown in Chart II. [b] The dimethylolurea copolymers (D) of the corresponding sulfonamide drugs have the structures P as noted below: $D_1 \equiv P_7$; $D_2 \equiv P_2$; $D_3 \equiv P_8$; $D_4 \equiv P_6$. [c] See Table I, footnotes *b* and *c*. [d] See Table I, footnote *d*.

CHART II



Looking at structures F_{1-4} and D_{1-4}, it is readily apparent that the weight per cent of sulfonamide moiety per repeat unit of the two copolymer systems varies considerably, and equal weights of any pair of analogous F and D copolymers would contain different quantities of sulfonamide comonomer. Thus, the display of data in Table II reinforces the conjecture that the observed antibacterial activity (obtained under identical test conditions) is not dependent *only* on the sulfonamide content of the copolymers.

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