New Compounds: Carbamate Derivatives of Mafenide (Homosulfanilamide)

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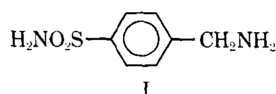
Abstract □ Carbamate derivatives of the aminomethyl group in mafenide (homosulfanilamide) were synthesized as potential antibacterial agents. None of the new compounds was active in antimicrobial or antiviral screening.

Keyphrases □ Homosulfanilamide—carbamate derivatives synthesized as possible antibacterial agents □ Carbamates, derivatives of mafenide—synthesized as possible antibacterial agents □ Antibacterial agents, potential—synthesis of carbamate derivatives of mafenide □ Mafenide—carbamate derivatives synthesized as possible antibacterial agents

Homosulfanilamide[1] (I) is an antibiotic used in the treatment of slow-healing wounds (1, 2) and also for infections of the ear, nose, and throat (3). Unlike most sulfonamides, homosulfanilamide is not antagonized by *p*-aminobenzoic acid, indicating that its mechanism of action differs from that of compounds of the sulfanilamide type.

Although effective topically, homosulfanilamide is ineffective orally or parenterally, apparently due to the rapid oxidation of the drug by MAO to the inactive metabolite *p*-carboxybenzenesulfonamide (4). To preserve or prolong antibacterial activity, Hartles and Williams (5) protected the aminomethyl function with acyl groups which could be metabolically hydrolyzed to the active homosulfanilamide. The amido derivatives demonstrated only slight or no activity both *in vitro* and *in vivo*. Of the derivatives evaluated, the *N*-butyryl analog appeared to be the best potential therapeutic agent *in vivo*, since the compound was the most readily absorbed and then deacylated. The possibility thus exists that free homosulfanilamide may be released in therapeutic concentrations greater than usual if and when cleavage of the protecting group occurs. Because carbamates are generally more readily hydrolyzed than amides, a series of derivatives (II*a*–*d*) of homosulfanilamide was synthesized (Table I) in which the aminomethyl group was protected, with the objective of achieving reduced metabolism and greater therapeutic effectiveness.



None of the new compounds demonstrated activity in a tissue culture antiviral screen. Furthermore, no activity was observed in a broad spectrum antimicrobial test. Based on these results, *in vivo* testing was not performed.

EXPERIMENTAL[2]

All carbamates in Table I were prepared by condensation of I with the appropriate chloroformate at an initial pH of ~8.5. All purified compounds gave one spot on TLC. IR, NMR, and mass spectra for all compounds were as expected.

To an erlenmeyer flask containing sodium bicarbonate (0.2 mole, 16.8 g.) in about 300 ml. of water was added homosulfanilamide hydrochloride (0.1 mole, 22.5 g.). To this solution was added dropwise the appropriate chloroformate (0.1 mole) over 1 hr. During this addition period, constant agitation and a slow increase of temperature (to about 50°) were provided by an ultrasonicator. The reaction mixture was cooled and filtered; the product was washed once with 5% hydrochloric acid, with water until neutral, and several times with chloroform and was then dried in a vacuum desiccator containing anhydrous calcium sulfate[3]. Compounds II*a*–*c* were recrystallized from acetone–benzene (1:3), and II*d* was recrystallized from ethanol. Usually two or three crystallizations provided an analytical sample.

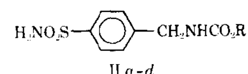


Table I—Carbamate Derivations of Homosulfanilamide

Compound	R	Formula	Yield, %[a]	Melting Point	Analysis, % Calc.	Analysis, % Found
II*a*	CH_3	$C_9H_{12}N_2O_4S$	44	165.5–166°	C 44.26	44.39
					H 4.92	4.93
					N 11.47	11.43
II*b*	CH_2CH_3	$C_{10}H_{14}N_2O_4S$	43	144.5–145°	C 46.51	46.57
					H 5.43	5.43
					N 10.85	10.81
II*c*	$CH_2C_6H_5$	$C_{15}H_{16}N_2O_4S$	64	160–160.5°	C 56.25	56.26
					H 5.00	5.04
					N 8.75	8.69
II*d*	C_6H_5	$C_{14}H_{14}N_2O_4S$	69	203–204°	C 54.90	54.67
					H 4.57	4.57
					N 9.15	9.13

[a] Crude product.

[1] Official USAN name is mafenide.

[2] Melting points were taken on a Thomas-Hoover apparatus and are corrected. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

[3] Drierite.

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COMMUNICATIONS

Inhibited Dissolution of Drug Crystals by Certified Water-Soluble Dyes: *In Vivo* Effect

Keyphrases ☐ Sulfathiazole dissolution—*in vivo* inhibition by water-soluble dye, man ☐ Dissolution, sulfathiazole—*in vivo* inhibition by water-soluble dye, man ☐ Dyes, water soluble—*in vivo* inhibition of sulfathiazole dissolution, man

Sir:

In previous articles, Piccolo and Tawashi (1–4) established the inhibitory effect of low concentrations of various water-soluble dyes on the dissolution rate of crystalline drugs. The effect of the degree of undersaturation, the effect of the nature of the dye, and the dependence of the dissolution rate on the dye concentration in powder systems were confirmed. The results obtained were discussed in the light of preferential adsorption of the dye molecules on the primary dissolution sources of the crystal surface. Further experiments were conducted to determine the influence of FD&C Blue No. 1 on the solubilizing effect by 0.04 *M* sodium cholate, using the sulfathiazole single crystal as a model substance. The data obtained showed that a concentration of only 5 mcg./ml. of the dye inhibited the dissolution rate to a value very close to that in distilled water (3). Since dissolution rate is often a rate-limiting step in the absorption of drugs with low aqueous solubility, and since micellar solubilization by bile salts plays an important role in the intestinal absorption of these drugs, the results obtained with certified water-soluble dyes are extremely interesting in relation to the drug absorption process. The present study was undertaken to examine the effect of FD&C Blue No. 1 on the absorption rate of sulfathiazole in man. Sulfathiazole Form I and FD&C Blue No. 1 were selected because they were tested *in vitro* previously (1, 3).

Three healthy young adult male human subjects were used in this study. One gram of sulfathiazole Form I crystals, 40 mesh USP, was suspended in 200 ml. of water and administered to each subject. Blood samples (0.2 ml., by finger puncture) were withdrawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 hr. following administration. After an interval of 1 week, a fresh suspension of 1 g. of sulfathiazole crystals in 200 ml. of water containing 10 mcg./ml. of FD&C Blue No. 1 (total quantity of dye is 2 mg.) was prepared and administered. Administration was in the morning to subjects in the fasting state, and no food was ingested until withdrawal of the last blood sample (5 hr.).

The blood samples (0.2 ml.) were diluted with 3 ml. of distilled water and precipitated with 0.8 ml. of 20% trichloroacetic acid. After centrifugation, the concentrations of free sulfathiazole were determined by the method of Bratton and Marshall (5), modified to use 2 ml. of the clear supernate (equal to 0.05 ml. of blood), 0.2 ml. of 1% sodium nitrite, 0.2 ml. of 0.5% ammonium sulfamate, and 1 ml. of 0.05% *N*-(1-naphthyl)ethyl-

Table I—Free Sulfathiazole Blood Concentrations for Three Subjects after Ingestion of 1 g. Oral Doses in the Absence and in the Presence of FD&C Blue No. 1

	Blood Concentrations, mg./100 ml.							
	Subject A		Subject B		Subject C		Mean Values	
Hours	Without Dye	With Dye	Without Dye	With Dye	Without Dye	With Dye	Without Dye	With Dye
0.5	0.285	0.116	0.381	0.174	0.254	0.000	0.307	0.097
1	0.793	0.445	0.841	0.237	0.444	0.175	0.693	0.286
1.5	0.888	0.889	1.412	0.365	0.746	0.635	1.015	0.630
2	1.349	1.064	1.412	0.936	1.047	0.746	1.236	0.915
2.5	1.793	0.873	1.190	0.984	1.206	0.826	1.396	0.894
3	1.555	1.064	1.174	1.158	1.270	0.937	1.333	1.053
4	1.714	1.032	1.365	1.444	1.190	1.588	1.423	1.355
5	2.418	1.127	2.016	1.571	1.254	1.635	1.896	1.444