ice bath to crystallization. The solid was filtered and recrystallized from the same solvent to give **2** as colorless crystals.

Method C. Homofarnesoylhydroxamic Acid (6).—The preparation was carried out according to method A but the reaction product, as obtained after evaporation of MeOH and extraction with Et_2O, was chromatographed on silica gel. Elution with C_6H_6 and mixtures of C_6H_6–Me_2CO furnished pure **6** as a colorless oil.

Nitrofuryl Heterocycles. IX.[1] Some Derivatives and Analogs of 6,7-Dihydro-3-(5-nitro-2-furyl)-5H-imidazo[2,1-*b*]thiazolium Chloride

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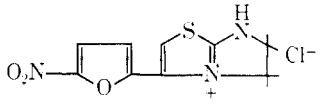
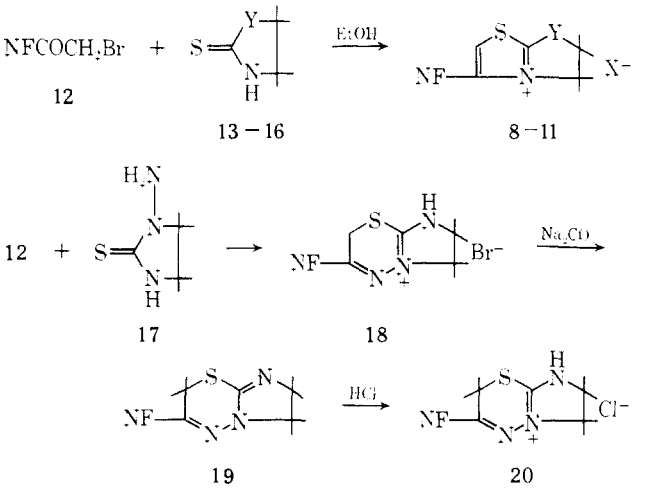
Since the discovery that furazolium chloride (**1**)[2] acted *in vitro* against *Proteus vulgaris* and *Pseudomonas aeruginosa* organisms, its use as a topical antibacterial agent has been investigated.[3] The synthesis of several derivatives and ring analogs of **1** is described and the *in vitro* testing data are reported.



1

Chemistry.—Compounds **4**–**7** are quaternary salts of 5,6-dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]thiazole (**2**),[3] the free base of **1**. These four compounds were prepared by treating **2** with the appropriate halide (**3a**–**d**) in a solvent such as Me_2CO or MeOH. Although assignment of position 7 for the alkyl group is arbitrary, alkylation at this position does result in an aromatic thiazole ring. Compounds **8**–**11** represent ring systems similar to **1** in which the imidazo portion has been substituted by a dihydrooxazole, dihydrothiazole, dihydropyrrole, and tetrahydropyridine, respectively. These compounds were prepared by the reaction of bromomethyl 5-nitro-2-furyl ketone **12**[4] with 2-thiooxazolidinone (**13**),[5] 2-thiazoline-2-thiol (**14**),[6] 2-thiopyrrolidone (**15**),[7] and 2-thiopiperiodone (**16**)[8] in ethanol, respectively (Scheme I). Compound **18** represents a ring system in which the thiazole ring of **1** has been replaced by a thiadiazine ring. The condensation of 1-amino-2-imidazolidinethione (**17**)[9] with **12** gave **18** which was converted to the chloride salt **20**.

SCHEME I



NF = 5-nitro-2-furyl

Screening Results.—The *in vitro* antibacterial activity data against *Staphylococcus aureus*, *Escherichia coli*, *P. aeruginosa*, *P. vulgaris*, *Salmonella typhosa*, *Streptococcus pyrogenes*, *Streptococcus agalactiae*, *Erysipelothrix insidiosa*, and *Aerobacter aerogenes*, given in Table I, were determined using methods described previously.[10] Data for **1** are induced for comparison. Many of the compounds possess broad-spectrum activity against both gram-positive and gram-negative organisms. However, none of the compounds showed the same level of activity against *P. aeruginosa* and *P. vulgaris* as that possessed by **1**.

Experimental Section[11]

6,7-Dihydro-7-methyl-3-(5-nitro-2-furyl)-5H-imidazo[2,1-*b*]-thiazolium Iodide (4).—A mixture of **12** (47.4 g, 0.2 mole), MeI (42.3 g, 0.3 mole), and Me_2CO (1000 ml) was heated at reflux for 1 hr. The color of the solution changed from deep red to a reddish brown and a brown solid separated. After cooling to room temperature, the solid was collected by filtration and dried at 65° to yield 60 g.

The filtrate was treated with additional MeI (21.2 g, 0.15 mole) and the above process was repeated. An additional amount of product (12 g) was obtained. The total yield of crude product was recrystallized from MeOH (55 ml/g) (charcoal) to give 50 g. An analytical sample was prepared by a further recrystallization from MeOH.

Compounds **5**–**7** were prepared by the above procedure using the appropriate benzyl bromide or iodide in MeOH. The products were purified by recrystallization from MeOH or $MeNO_2$.

2,3-Dihydro-5-(5-nitro-2-furyl)thiazolo[2,3-*b*]oxazolium Bromide (8).—A mixture of **12** (125 g, 0.533 mole), **13** (48.5 g, 0.533 mole), and absolute EtOH (1100 ml) was refluxed for 4 hr. The reaction mixture was cooled and filtered to yield 80.0 g of product. The material was recrystallized (charcoal) from MeOH.

2,3-Dihydro-5-(5-nitro-2-furyl)thiazolo[2,3-*b*]thiazolium Chloride (9).—Compound **12** (46.8 g, 0.2 mole) was added to a solution of **14** (23.8 g, 0.2 mole) in Me_2CO (500 ml) at room

(1) For paper VIII in this series see H. A. Burch, *J. Med. Chem.*, **12**, 535 (1969).

(2) Novafur®, Dermafur®, 6,7-dihydro-3-(5-nitro-2-furyl)-5H-imidazo-[2,1-*b*]thiazolium chloride.

(3) H. R. Snyder, Jr., and L. E. Benjamin, *J. Med. Chem.*, **9**, 402 (1966); R. Freedman and R. E. Chamberlain, "Antimicrobial Agents and Chemotherapy—1967," G. L. Hobby, Ed., American Society for Microbiology, Ann Arbor, Mich., 1968, p 502; H. E. Russell, D. P. Gutekunst, and R. E. Chamberlain, *ibid.*, p. 497; N. Georgiade, M. Lucas, R. Georgiade, and W. Garrett, *Plastic Reconstruc. Surg.*, **39**, 349 (1967); D. E. Bidlack, *Vet. Med.*, **62**, 1070 (1967); R. L. Brutus, *Animal Hosp.*, **3**, 206 (1967); R. S. Titus, *Southwestern Vet.* **20**, 295 (1967).

(4) O. Dann, H. Ulrich, and E. F. Moller, *Z. Naturforsch.*, **7b**, 334 (1952); *Chem. Abstr.*, **47**, 8730*f* (1953).

(5) A. A. Rosen, *J. Am. Chem. Soc.*, **74**, 2994 (1952).

(6) Purchased from Matheson Coleman and Bell Co.

(7) J. Tafel and P. Lawaczek, *Ber.*, **40**, 2842 (1907).

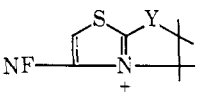
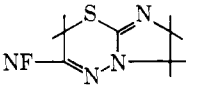
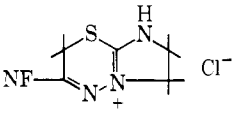
(8) J. Renault, *Bull. Soc. Chim. France*, 1001 (1953).

(9) S. Szoke, P. Szentmiklosi, G. Kormoczy, A. David, G. Horvath, and S. Ritter, Hungarian Patent 152,194 (1965); *Chem. Abstr.*, **63**, 13274 (1965).

(10) F. F. Ebetino, W. F. Cary, and B. F. Stevenson, *J. Med. Chem.*, **6**, 633 (1963).

(11) All melting points were taken on a micro hot stage (Fisher-Johns) melting apparatus and are uncorrected. The analyses are indicated in Table I; the analytical results obtained for those elements were within ±0.4% of the theoretical values.

TABLE I

No.	Y	X	Yield, %	Mp, °C	Formula	MIC, μg/ml[a] S. aureus Mi-6[b]	E. coli Es-2	P. aeruginosa Ps-10	P. vulgaris Pr-12	S. typhosa SaD-13	S. pyogenes StA-1	S. agalactiae StB-12	E. insidiosa Er-4	A. aerogenes Ae-6
	 X⁻ (NF = 5-nitro-2-furyl)													
1	NH	Cl				6.25	<0.75	25	25	<0.75	6.25	25	1.5	3.1
4	NCH_3	I	95	248–249	$C_{10}H_{10}IN_3O_3S$[c]	12.5	100	>200	>200	100	50	100	25	>200
5	$NCH_2C_6H_5$	Br	79	247–247.5	$C_{16}H_{14}BrN_3O_3S$[d]	3.1	12.5	>200	>200	25	1.5	6.25	3.1	100
6	$NCH_2C_6H_4Cl$-*p*	I	80	216–217	$C_{16}H_{13}ClIN_3O_3S$[e]	3.1	12.5	>200	>200	50	1.5	12.5	6.25	>200
7	$NCH_2C_6H_3Cl_2$-2,4	I	72	222–223	$C_{16}H_{12}Cl_2IN_3O_3S$[e]	3.1	12.5	>200	>200	25	6.25	6.25	6.25	>200
8	O	Br	47	151–152	$C_9H_7BrN_2O_4S$[d]	25	1.5	>50	>50	3.1	25	>50	>50	>50
9	S	Cl	80	240–241	$C_9H_7ClN_2O_3S_2$[f]	>200	>200	>200	>200	>200	>200	>200	>200	>200
10	CH_2	Br	60	228–229	$C_{10}H_9BrN_2O_3S$[d]	>200	>200	>200	>200	>200	50	100	100	>200
11	CH_2CH_2	Br	72	205–206	$C_{11}H_{11}BrN_2O_3S$[d]	50	200	>200	>200	>200	50	100	50	>200
														
19			81	174–175	$C_9H_8N_4O_3S$[g]	12.5	1.5	>200	200	3.1	12.5	25	50	100
														
20			88	235 dec	$C_9H_9ClN_4O_3S$[h]	12.5	1.5	>100	>100	12.5	12.5	12.5	12.5	100

[a] Minimal inhibitory concentration is the lowest concentration of a compound that prevents growth visible after 24 hr of incubation. [b] The Norwich Pharmacal Co. strain number. [c] *Anal.* C, H, I. [d] *Anal.* C, H, Br, S. [e] *Anal.* C, H, I, N. [f] *Anal.* C, H, Cl, N, S. [g] *Anal.* C, H, N. [h] *Anal.* C, H, Cl, S.

temperature. After several hours, the mixture was filtered. The crude material was added to concentrated HCl (500 ml) and the mixture was diluted with *i*-PrOH, cooled, and filtered. The yellow needles were washed with *i*-PrOH and Et_2O and dried at 100° to give 46 g of **9**. The material was recrystallized from 3 *N* HCl to yield 37 g. The product became light sensitive after drying at 100°.

6,7-Dihydro-3-(5-nitro-2-furyl)-5H-pyrrolo[2,1-*b*]thiazolium Bromide (10).—A mixture of **12** (58.5 g, 0.25 mole) and **15** (23.5 g, 0.25 mole) in absolute EtOH (600 ml) was heated to reflux. A nearly colorless solid separated and redissolved after *ca.* 10 min of refluxing. Reflux was continued, with stirrring, for a total of 30 min. Decolorizing charcoal was added during the last 10 min and then the hot solution was filtered by suction. The filtrate was cooled and filtered to give 48 g of product melting at *ca.* 220° with previous darkening. The crude product was boiled with Me_2CO and filtered to yield a light tan solid (46 g). The material was recrystallized from absolute EtOH (15 ml/g) to give 35 g of **10** as tan platelets.

3-(5-Nitro-2-furyl)-5,6,7,8-tetrahydrothiazolo[3,2-*a*]pyridinium Bromide (11).—A mixture of 12 (46.8 g, 0.2 mole) and **16** (23 g, 0.2 mole) in absolute EtOH (470 ml) was heated at reflux with stirring for 1 hr. A solid separated initially but redissolved on continued heating. The solution was evaporated to one-half volume, *in vacuo*, cooled, and diluted with Et_2O (300 ml). After standing at room temperature for several hours with occasional scratching, a solid separated. The product was collected, washed with ether, and dried to give 47.5 g of a green solid. The material was recrystallized from *i*-PrOH (40 ml/g) in the dark (compound is light sensitive) to yield **11** as a beige solid.

6,7-Dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]-1,3,4-thiadiazine (19).—A mixture of **12** (46.8 g, 0.2 mole) and **17**[12] in absolute EtOH (225 ml) was heated at reflux for 15 min. Complete solution occurred and then a yellow solid separated. The mixture was cooled and filtered to give crude **16**. The crude material was dissolved in hot H_2O (600 ml), treated with charcoal, and filtered. The filtrate was cooled to *ca.* 70° and made basic with aqueous Na_2CO_3. After cooling in an ice bath, the brownish orange solid was collected, washed with H_2O, and dried at 100° to yield 41 g of **19**. The crude material was recrystallized from MeOH (60 ml/g) to yield orange needles after cooling slowly to room temperature.

7,8-Dihydro-3-(5-nitro-2-furyl)-6H-imidazo[2,1-*b*]-1,3,4-thiadiazinium Chloride (20).—A hot solution of **19** (28 g, mole) 0.11 in MeOH (1800 ml) was treated with charcoal and filtered. Dry HCl was passed into the filtrate until the solution was strongly acidic. The product separated as a yellow solid after the solution was diluted with Et_2O (600 ml) and cooled in an ice bath for several hours. A yield of 29 g of product was obtained which decomposed at 235°. An analytical sample was obtained by several recrystallizations from 2 *N* HCl (20 ml/g).

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(12) Although **17** was prepared by the procedure given in ref 9, the product obtained melted at 179–181° (lit.[9] 114°). *Anal.* ($C_3H_7N_3S$) C, H, S.