Compound **3** displayed practically no antitumor activity against Sarcoma 180 and mouse Ehrlich ascites; its acute LD_{50} on mice was 8.4 mg/kg ip.

Experimental Section

Melting points are uncorrected. Microanalyses are indicated only by symbols of the elements; unless otherwise stated, analytical results were within ±0.4% of the theoretical values. The uv absorption spectra were measured on an Optica CF 4 spectrometer. Ir spectra were recorded on a Perkin-Elmer 21 spectrometer.

5,8-Dihydroxyquinazoline (2).—A mixture of 4.5 g (23.7 mmoles) of 5,8-dimethoxyquinazoline (**1**) and 20 g (150 mmoles) of anhydrous $AlCl_3$ was heated in an oil bath at 170–180° for 8 hr. The reaction mixture was dissolved in 200 ml of H_2O and the solution was extracted with Et_2O (six 500-ml portions). The combined yellow extracts, which were dried (Na_2SO_4) and distilled at atmospheric pressure, yielded 1.08 g of a yellow solid which was sublimed *in vacuo* (0.001 mm). The fraction which sublimed below 140° was discarded, while the crystalline product which sublimed between 160 and 170° was crystallized from EtOAc; yield 0.48 g (12.5%) of yellow needles: mp 253°; λ_{max}^{EtOH} 205 nm (log ε 4.21), 249 (4.46), 340 (3.49); ν_{max} (KBr) 3455 (OH) and 1028 cm^{-1}. *Anal.* ($C_8H_6N_2O_2$) C, H, N.

Physical Measurements.—The acid ionization constant of **2** was determined by potentiometric titration:[10] pK_a (acid) at 20°, 8.4. The stability constants of metal complexes of **2** were determined by potentiometric titrations[9a,c,d] With Cu^{2+}, log $K' = 9.8$; with Co^{2+}, log $K' = 8.0$.

The partition coefficient in oleyl alcohol-H_2O was determined according to the method of Albert and Hampton:[9a] at 20°, the value is 0.33.

5,8-Quinazolinedione (3).—To an ice-cold stirred solution of 0.5 g (3.1 mmoles) of 5,8-dihydroxyquinazoline (**2**) in 50 ml of 10% H_2SO_4 was added a solution of 0.35 g (1.2 mmoles) of $K_2Cr_2O_7$ in 6 ml of H_2O. The solution was stirred with cooling (ice bath) for 45 min and extracted with $CHCl_3$ (five 300-ml portions). After distillation of the solvent at atmospheric pressure, the residue, crystallized three times from C_6H_6–petroleum ether (bp 30–50°) (1:1) yielded 0.37 g (74.9%) of a crystalline yellow-brown substance which decomposed, without melting, above 350°; λ_{max}^{EtOH} 205 nm (log ε 4.21), 249 (4.33), 325 (3.40), 341 (3.49); ν_{max} 1678 (C=O), 1575 cm^{-1}. *Anal.* ($C_8H_4N_2O_2$) C, H, N.

The quinhydrone of 2 and 3 was prepared by mixing separate solutions containing 25 mg each of **2** and **3** dissolved in 5 ml of PhMe. After standing in the cold, red-brown crystals formed, mp 318°. *Anal.* ($C_{16}H_{10}N_2O_4$) H, N; C: calcd, 59.63; found, 58.83.

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Terpene Compounds as Drugs. VII. Terpenylhydroxamic Acids

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Hydroxamic acids possess biologic effects which include a particularly valuable antifungal activity.[1] As part of our program in the field of terpene compounds, we have prepared a series of terpenylhydroxamic acids and tested their antifungal properties. A report[2] on a possible therapeutic application of the urease inhibitory effect of hydroxamic acids[3] prompted us to test our compounds for this activity as well. The compounds were prepared by reaction of NH_2OH with the appropriate carboxylic ester; their chemical data are listed in Table I.

Antifungal activity was evaluated against four fungi according to a method previously described;[4] for comparative purposes 10-undecenohydroxamic acid (**10**) and nystatin were assayed concurrently. The results, reported in Table II, indicate that only compounds derived from sesquiterpenes displayed interesting antifungal activity; among them **6**, which proved as active as nystatin, appears to be worthy of a more detailed study. The inhibitory effect of terpenylhydroxamic acids on bacterial urease *in vitro* was tested, in comparison with acetohydroxamic acid, according to a new procedure.[5] The enzyme was incubated at 37° in a solution of urea in phosphate buffer with addition of the test compound. After 20 and 30 min, NH_3 liberated by the enzyme was assayed according to the method of McCullough.[6] The inhibitions, reported in Table III, were calculated for control tests performed without any addition of compounds. Potency of **3** and **9** *in vitro* was comparable with that of acetohydroxamic acid; **4** was less active, whereas other compounds were inactive. Compounds **3**, **4**, **9**, and acetohydroxamic acid were tested on hyperammonemia induced by intraperitoneal injections of urea (200 mg/kg) and urease (25 mg/kg) in rats.[5] Acetohydroxamic acid, at a dose of 100 mg/kg orally, significantly reduced blood NH_3 2, 4, 6, and 8 hr after urea–urease injections; compounds **3**, **4**, and **9**, tested at the same dose, exhibited no activity.

Experimental Section[7]

Method A. Geranoylhydroxamic Acid (1).—A solution of NaOH (12.4 g, 0.36 mole) in 50% MeOH (50 ml) was added at 10–15° with stirring under N_2 to $NH_2OH \cdot HCl$ (18.1 g, 0.26 mole) dissolved in H_2O (23 ml). Methyl geranate (36.5 g, 0.2 mole) was subsequently added and the mixture was stirred for 6 hr at room temperature. Acidification to pH 2–3 with 15% HCl and evaporation of MeOH at reduced pressure gave a suspension which was extracted with Et_2O. The Et_2O layer was extracted with 3% NaOH and the alkaline solution was acidified with 15% HCl to give an oil which was extracted with Et_2O and dried ($MgSO_4$). Evaporation of the solvent gave a residue (10.2 g) of crude **1**. This product, dissolved in AcOH (15 ml), was dropped with vigorous stirring into a solution of copper acetate (16.6 g, 0.083 mole) in H_2O (230 ml). The green gummy precipitate was thoroughly washed (H_2O, absolute EtOH), filtered, and dried. The solid obtained was then shaken with Et_2O (300 ml) and 25% H_2SO_4 (100 ml) to complete dissolution. The Et_2O layer, washed (H_2O) and dried (Na_2SO_4), was evaporated to give 5.5 g of **1** as a colorless oil.

Method B. Citronelloylhydroxamic Acid (2).—Crude citronelloylhydroxamic acid (prepared according to method A) was taken up in petroleum ether (bp 40–70°) and allowed to stand in an

(1) (a) H. Kitagawa, S. Yoshida, M. Abe, W. C. Chen, and T. Arai, *J. Pharm. Soc. Jap.*, **85**, 860 (1965); (b) R. M. Patel, D. P. Carew, and J. L. Lach, *J. Pharm. Sci.*, **56**, 1326 (1967).

(2) W. N. Fishbein, P. P. Carbone, and H. D. Hochstein, *Nature*, **208**, 46 (1965).

(3) K. Kobashi, J. Hase, and K. Uehara, *Biochim. Biophys. Acta*, **65**, 380 (1962).

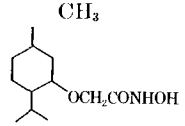
(4) G. Coppi, A. Maselli, and C. Ciani-Bonardi, *Farmaco, Ed. Sci.*, **20**, 203 (1965).

(5) G. Coppi and G. Bonardi, manuscript in preparation.

(6) H. McCullough, *Clin. Chim. Acta*, **17**, 297 (1967).

(7) Melting points are corrected and were taken on a Büchi capillary melting point apparatus. Purity of compounds was checked by tlc, ir, and nmr.

TABLE I: TERPENYLHYDROXAMIC ACIDS

Compd	Name	Structure	Method	Yield,[a] %	Mp, °C	Formula[b]
1	Geranoylhydroxamic acid	$CH_3C(CH_3)=CHCH_2CH_2C(CH_3)=CHCONHOH$	A	15	Oil[c]	$C_{10}H_{17}NO_2$
2	Citronelloylhydroxamic acid	$CH_3C(CH_3)=CHCH_2CH_2CH(CH_3)CH_2CONHOH$	B	22[d]	74–75[e]	$C_{10}H_{19}NO_2$
3	Homogeranoylhydroxamic acid	$CH_3C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2CONHOH$	B	20[d]	73–74	$C_{10}H_{19}NO_2$
4	Geranylacetylhydroxamic acid	$CH_3(C(CH_3)=CHCH_2CH_2)_2CONHOH$	B	41[d]	81–82	$C_{12}H_{21}NO_2$
5	Farnesoylhydroxamic acid	$CH_3(C(CH_3)=CHCH_2CH_2)_2C(CH_3)=CHCONHOH$	A	16	Oil	$C_{13}H_{23}NO_2$
6	Homofarnesoylhydroxamic acid	$CH_3(C(CH_3)=CHCH_2CH_2)_2C(CH_3)=CHCH_2CONHOH$	C	28	Oil	$C_{16}H_{27}NO_2$
7	Farnesylacetylhydroxamic acid	$CH_3(C(CH_3)=CHCH_2CH_2)_3CONHOH$	A	19	Wax	$C_{17}H_{29}NO_2$
8	Geranylgeranoylhydroxamic acid	$CH_3(C(CH_3)=CHCH_2CH_2)_3C(CH_3)=CHCONHOH$	A	30	Oil	$C_{22}H_{37}NO_2$
9	Menthoxyacetylhydroxamic acid		B	40[d]	69–70	$C_{12}H_{23}NO_3$

[a] Crystallized or purified product. [b] All compounds were analyzed for C, H, N; the analytical values were within ±0.4% of the theoretical values. [c] Previously prepared by another method by G. Velardi, *Gazz. Chim. Ital.*, **34** (II), 66 (1904). [d] Crystallized from petroleum ether (bp 40–70°). [e] Lit.[c] mp 72–74°.

TABLE II: *In Vitro* ANTIFUNGAL ACTIVITY[a]

	Min inhib concn, μg/ml			
Compd	*Candida albicans* DM	*S. cerevisiae* ATCC 9763	*T.* ATCC 8757	*Cryptococcus neoformans* 18M
1	80	40	20	80
2	>80	>80	>80	>80
3	80	80	80	80
4	40	40	20	40
5	10	5	5	10
6	0.62	2.5	5	0.62
7	2.5	10	5	10
8	40	40	>80	>80
9	>80	>80	>80	80
10	5	5	10	2.5
Nystatin	1.25	1.25	5	1.25

[a] *S.* = *Saccharomyces*; *T* = *Tricophyton mentagrophytes*.

TABLE III: *In Vitro* INHIBITION OF UREASE

	% inhib[a]	
Compd	20 min	30 min
1	7.5	3.7
2	6.8	12.0
3	39.4	52.0
4	23.4	26.0
5	16.6	0.0
6	4.4	4.6
7	12.6	14.6
8	11.4	6.4
9	49.2	49.6
Acetohydroxamic acid	45.0	44.0

[a] Inhibitor concentration 0.01%.

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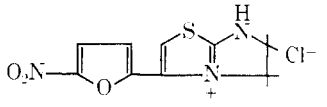
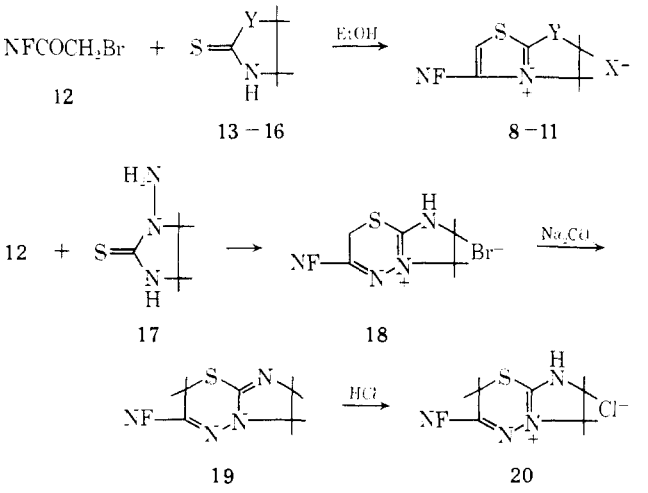
Since the discovery that furazolium chloride (**1**)[2] acted *in vitro* against *Proteus vulgaris* and *Pseudomonas aeruginosa* organisms, its use as a topical antibacterial agent has been investigated.[3] The synthesis of several derivatives and ring analogs of **1** is described and the *in vitro*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

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(6) Purchased from Matheson Coleman and Bell Co.

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(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.