and:

$$\text{rate} = \left[\frac{Al}{2}\left(\frac{dQ}{dt}\right)_{ss}\right]^{1/2} t^{-1/2} \qquad \text{(Eq. 6)}$$

where $(dQ/dt)_{ss}$ is the slope of the steady-state portion of the curve from a diffusion cell experiment (Fig. 5) and the other terms are as were defined. This approach is valuable in screening compounds to assess whether release rates are consistent with their biological dosing patterns.

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NOTES

Synthesis and Antibacterial and Antifungal Activities of Alkyl and Polyhalophenyl Esters of Benzo[*b*]thiophene-3-carbamic Acid

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Abstract □ Several alkyl and polyhalophenyl esters of benzo[*b*]thiophene-3-carbamic acid were prepared and tested for antibacterial and antifungal activities. Two compounds exhibited the highest activity of growth inhibition against some bacteria and fungi.

Keyphrases □ Antibacterial activity—alkyl and polyhalophenyl esters of benzo[*b*]thiophene-3-carbamic acid □ Antifungal activity—alkyl and polyhalophenyl esters of benzo[*b*]thiophene-3-carbamic acid □ Benzo[*b*]thiophene-3-carbamic acid—alkyl and polyhalophenyl esters, synthesis, antibacterial and antifungal activities

Dialkylaminoalkyl esters of benzo[*b*]thiophene-2-carboxylic acid[1] reportedly are useful as hypotensive, antiviral, and antifungal agents (1). Derivatives of benzo[*b*]thiophene-2-carboxamide were reported to have local anesthetic and analgesic activities (2). Some carbamic acids having the benzo[*b*]thiophene moiety showed pesticidal, fungicidal, and insecticidal activities (3).

In continuing studies on the chemistry and antibacterial and fungicidal activities of carbamic acid esters (4–7), alkyl and polyhalophenyl esters of benzo[*b*]thiophene-3-carbamic acid were synthesized and their efficacy was determined.

DISCUSSION

Chemistry—The desired compounds were prepared according to Scheme I.

The reaction of *N*-bromosuccinimide with readily available 3-chloromethylbenzo[*b*]thiophene (I) (8) afforded II. Hydrolysis of II gave benzo[*b*]thiophene-3-carboxylic acid (III) (9). Compound III was converted to benzo[*b*]thiophene-3-carboxyhydrazide (V) by a literature method (10). The hydrazide (V) then was transformed to the carboxazide (VI) by reaction with sodium nitrite in acetic acid. Curtius rearrangement of the azide was achieved readily through heating with alcohols or with polyhalophenols in refluxing benzene. The physical data of the compounds prepared are summarized in Table I.

Antifungal and Antibacterial Activities—All compounds listed in Table I were tested against *Candida albicans* (28012), *Penicillium not-*

[1] Benzo[*b*]thiophene also is known as thianaphthene.

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Table I—Physical Constants of Benzo[*b*]thiophene-3-carbamic Acid Esters

Compound	R	Yield, %	Melting Point[a]	Formula	Analysis, %	Calc.	Found
VII*a*	CH_3	82	63–65°	$C_{10}H_9NO_2S$	C	57.97	57.73
					H	4.35	4.51
					N	6.76	6.95
VII*b*	C_2H_5	80	67–70°	$C_{11}H_{11}NO_2S$	C	59.73	59.91
					H	4.98	4.79
					N	6.33	6.51
VII*c*	n-C_3H_7	75	56–58°	$C_{12}H_{13}NO_2S$	C	61.28	61.09
					H	5.53	5.38
					N	5.96	6.18
VII*d*	n-C_4H_9	80	70–73°	$C_{13}H_{15}NO_2S$	C	62.65	62.84
					H	6.02	5.89
					N	5.62	5.43
VII*e*	n-C_6H_{13}	75	55–57°	$C_{15}H_{19}NO_2S$	C	64.98	64.79
					H	6.86	6.63
					N	5.05	4.88
VII*f*	Cyclohexyl	75	95–97°	$C_{15}H_{17}NO_2S$	C	65.45	65.27
					H	6.18	6.02
					N	5.09	4.93
VII*g*	C_6H_5	60	103–105°	$C_{15}H_{11}NO_2S$	C	66.91	66.72
					H	4.09	4.28
					N	5.20	5.38
VII*h*	o-ClC_6H_4	85	142–144°	$C_{15}H_{10}ClNO_2S$	C	59.31	59.50
					H	3.29	3.48
					N	4.61	4.82
VII*i*	m-ClC_6H_4	85	114–116°	$C_{15}H_{10}ClNO_2S$	C	59.31	59.12
					H	3.29	3.46
					N	4.61	4.52
VII*j*	p-ClC_6H_4	80	131–133°	$C_{15}H_{10}ClNO_2S$	C	59.31	59.50
					H	3.29	3.46
					N	4.61	4.48
VII*k*	p-BrC_6H_4	65	138–140°	$C_{15}H_{10}BrNO_2S$	C	51.72	51.53
					H	2.87	2.64
					N	4.02	3.85
VII*l*	2,3-Dichlorophenyl	45	125–127°	$C_{15}H_9Cl_2NO_2S$	C	53.25	53.44
					H	2.66	2.84
					N	4.14	4.32
VII*m*	2,4-Dichlorophenyl	45	164–166°	$C_{15}H_9Cl_2NO_2S$	C	53.25	53.05
					H	2.66	2.84
					N	4.14	4.02
VII*n*	2,6-Dichlorophenyl	45	152–154°	$C_{15}H_9Cl_2NO_2S$	C	53.25	53.15
					H	2.66	2.84
					N	4.14	4.32
VII*o*	2,4,5-Trichlorophenyl	80	170–172°	$C_{15}H_8Cl_3NO_2S$	C	48.32	48.15
					H	2.15	2.02
					N	3.76	3.89
VII*p*	2,4,6-Trichlorophenyl	65	160–162°	$C_{15}H_8Cl_3NO_2S$	C	48.32	48.51
					H	2.15	2.37
					N	3.76	3.65
VII*q*	2,4,6-Tribromophenyl	60	172–174°	$C_{15}H_8Br_3NO_2S$	C	35.57	35.74
					H	1.58	1.79
					N	2.77	2.96
VII*r*	Pentachlorophenyl	62	160–162°	$C_{15}H_6Cl_5NO_2S$	C	40.77	40.56
					H	1.36	1.17
					N	3.17	3.39

[a] All compounds were crystallized from ether–petroleum ether.

atum (S-13), and *Aspergillus niger* (23171) *in vitro* using Sabouraud dextrose agar medium[2].

Each compound was dissolved in acetone to a concentration of 1 mg/ml. These solutions were diluted with hot culture medium to the desired concentrations and autoclaved at 120° for 2 hr. Five replicates of each concentration were prepared. The antifungal activity of all compounds tested, except VII*o* and VII*r*, was insignificant at a concentration of 10 μg/ml against *A. niger* and *C. albicans*, while most compounds were effective at this concentration against *P. notatum*. Griseofulvin was used as a control (Table II).

All compounds also were tested against *Bacillus subtilis* (NCTC 3610), *Staphylococcus aureus* (ATCC 6538), and *Escherichia coli* (ATCC 10536). Nitrofurantoin was used as a control. The compounds were dissolved in dimethylformamide and diluted to a 0.5% concentration. Standard paper disks with a 6-mm diameter were immersed in the solution and were placed on the inoculated assay medium surface[3].

All of the compounds tested, except VII*o* and VII*r*, had insignificant antibacterial activity against *S. aureus*. Compounds VII*m* and VII*o*–VII*r* exhibited moderate activity against *B. subtilis*. The activity of VII*o*, VII*q*, and VII*r* against *E. coli* was significant (Table III).

EXPERIMENTAL[4]

Benzo[*b*]thiophene-3-carboxylic Acid (III)—A mixture of I (18.25 g, 0.1 mole) and *N*-bromosuccinimide (35.6 g, 0.2 mole) in 250 ml of carbon tetrachloride was irradiated with a 500-w lamp[5] while heating and stirring at reflux temperature for 4 hr. Then the reaction mixture was cooled and filtered, and the solvent was evaporated. The residue was made alkaline with 300 ml of 10% sodium carbonate solution and was heated with stirring on a steam bath for 2 hr. The mixture was cooled and extracted with 200 ml of benzene. Acidification of the aqueous sodium carbonate portion with 6 *N* HCl gave a precipitate. This precipitate was filtered and crystallized from benzene to give 4.4 g (55% yield) of III, mp 175–176° [lit. (9) mp 175–176°].

[2] These microorganisms were obtained from the Department of Parasitology, Public Health Institute, Tehran, Iran.

[3] BP (1968) antibiotic assay medium.

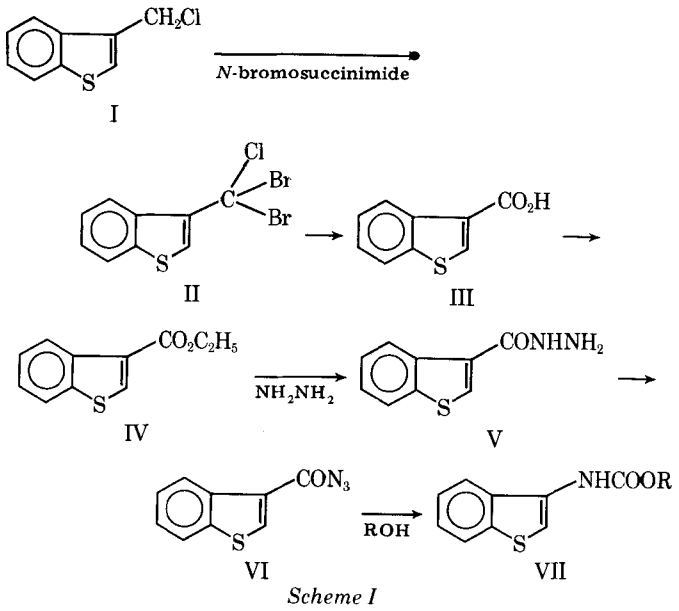
[4] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded using a Perkin-Elmer 267 spectrometer. NMR spectra were determined with a Varian T-60A instrument. Mass spectra were recorded on a Varian Mat III instrument.

[5] General Electric photospot lamp.

Table II—Antifungal Activity [a] of Benzo[*b*]thiophene-3-carbamic Acid Esters

Compound	*A. niger*			*C. albicans*			*P. notatum*		
	10 μg/ml	20 μg/ml	50 μg/ml	10 μg/ml	20 μg/ml	50 μg/ml	10 μg/ml	20 μg/ml	50 μg/ml
VII*a*	−	−	+	−	−	+	−	+	+
VII*b*	−	−	+	−	−	+	−	+	+
VII*c*	−	−	+	−	−	+	−	−	+
VII*d*	−	−	+	−	−	+	−	+	+
VII*e*	−	−	+	−	−	+	−	−	+
VII*f*	−	−	+	−	−	+	+	+	+
VII*g*	−	−	+	−	−	+	+	+	+
VII*h*	−	−	+	−	−	+	−	+	+
VII*i*	−	−	+	−	−	−	−	−	+
VII*j*	−	−	+	−	−	+	+	+	+
VII*k*	−	−	+	−	−	−	−	−	+
VII*l*	−	−	+	−	−	+	−	+	+
VII*m*	−	−	+	−	−	+	−	+	+
VII*n*	−	−	+	−	−	+	+	+	+
VII*o*	+	+	+	+	+	+	+	+	+
VII*p*	−	+	+	−	+	+	+	+	+
VII*q*	−	+	+	−	+	+	+	+	+
VII*r*	+	+	+	+	+	+	+	+	+
Griseofulvin	−	−	+	−	−	+	−	+	+

[a] Key: + = complete inhibition and − = no inhibition.



Scheme I

Benzo[*b*]thiophene-3-carboxazide (VI)—To a stirring solution of V (19.2 g, 0.1 mole) (10) in 200 ml of 50% acetic acid at 0° was added dropwise a solution of sodium nitrite (6.9 g, 0.1 mole) in 100 ml of water. The reaction mixture was stirred for an additional 30 min. The precipitate was filtered, washed with water, dried at room temperature under reduced pressure, and crystallized from ether–petroleum ether to give 4 g (76% yield) of VI, mp 103–105°; IR (KBr): 2170 (azide) cm^{-1}.

Anal.—Calc. for $C_9H_5N_3OS$: C, 53.20; H, 2.46; N, 20.69. Found: C, 53.45; H, 2.64; N, 20.85.

Methyl Benzo[*b*]thiophene-3-carbamate (VII*a*)—A solution of VI (2.03 g, 0.01 mole) in 20 ml of methanol was refluxed for 6 hr. The solvent was evaporated, and the residue was crystallized from ether–petroleum ether to give 1.70 g (82% yield) of VII*a*, mp 63–65°; IR (KBr): 3340 (NH) and 1700 (ester) cm^{-1}; NMR ($CDCl_3$): δ 8.10–7.33 (m, 5H, aromatic), 7.05 (broad s, 1H, NH), and 3.85 (s, 3H, OCH_3) ppm; mass spectrum: *m/z* (relative intensity) 207 (M^+, 100), 175 (57), 148 (39), and 121 (39).

Anal.—Calc. for $C_{10}H_9NO_2S$: C, 57.97; H, 4.35; N, 6.76. Found: C, 57.73; H, 4.51; N, 6.95.

Compounds VII*b*–VII*f* were prepared similarly (Table I).

Phenyl Benzo[*b*]thiophene-3-carbamate (VII*g*)—A solution of VI (2.03 g, 0.01 mole) and phenol (0.94 g, 0.01 mole) in 30 ml of dry benzene was refluxed for 5 hr, and the mixture then was filtered. The solvent was evaporated, and the residue was crystallized from ether–petroleum ether to give 1.61 g (60% yield) of VII*g*, mp 103–105°; IR (KBr): 3280 (NH) and 1710 (CO) cm^{-1}.

Anal.—Calc. for $C_{15}H_{11}NO_2S$: C, 66.91; H, 4.09; N, 5.20. Found: C, 66.72; H, 4.28; N, 5.38.

Compounds VII*h*–VII*r* were prepared similarly (Table I).

Table III—Antibacterial Activity [a] of Benzo[*b*]thiophene-3-carbamic Acid Esters

Compound	Average Inhibition Zone Diameter, mm		
	E. coli	*S. aureus*	*B. subtilis*
VII*a*	−	−	−
VII*b*	−	−	−
VII*c*	−	14	10
VII*d*	−	−	−
VII*e*	−	−	−
VII*f*	−	12	−
VII*g*	−	8	12
VII*h*	12	−	−
VII*i*	8	−	−
VII*j*	−	−	−
VII*k*	−	−	−
VII*l*	−	−	−
VII*m*	−	−	20
VII*n*	−	−	−
VII*o*	22	17	15
VII*p*	11	−	15
VII*q*	24	−	20
VII*r*	30	24	20
Nitrofurantoin	25	25	25

[a] Key: − = inactive.

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