salt), was reported by Åkerfeldt[8] to provide 80% protection at the maximum tolerated dose. Compound **11**, having a four-carbon backbone, lacked effectiveness.

A comparison of the radioprotective activities of aminoalkanethiosulfuric acids with the corresponding substituted or unsubstituted guanidinoalkanethiosulfuric acids revealed that superior activity is obtained if the guanidino group is unsubstituted. Diminished activity results, however, if the guanidino moieties are alkyl-substituted. As was the case with aminoalkanethiosulfuric acids,[1] optimal effectiveness is found in guanidinoalkanethiosulfuric acids when the N and S functions are separated by two carbon atoms.

Experimental Section[12]

2-Methyl-2-thiopseudourea Iodides.—An EtOH solution of a thiourea was heated under reflux with 1.1 equiv of MeI for *ca.* 0.5 hr. Evaporation of the solvent under reduced pressure gave the 2-methyl-2-thiopseudourea iodide in high yield. Purification was usually achieved by recrystallization of the product from EtOH–Et_2O.

Guanidinoalkanethiosulfuric Acids.—This general procedure is a modification of one described by Kaluszyner.[4] To an aqueous solution containing 1 equiv of a 2-methyl-2-thiopseudourea iodide (or sulfate) was slowly added with stirring an aqueous solution of 1 equiv of an aminoalkanethiosulfuric acid and 1 equiv of NaOH. When addition was complete, the resultant solution was heated on a steam bath until the evolution of MeSH virtually ceased. The latter was detected as a yellow lead mercaptide by holding a piece of filter paper spotted with $Pb(OAc)_2$ near the mouth of the flask. The solution was concentrated at reduced pressure and cooled causing the separation of the product. The guanidinoalkanethiosulfuric acid was recrystallized until free of I^- (or SO_4^{2-}).

2-Aminobutane-1-thiosulfuric Acid.—A solution of 23.3 g (0.1 mole) of 2-amino-1-bromobutane hydrobromide, prepared by the reaction of 48% HBr with 2-aminobutanol according to the method of Cortese,[13] and 24.8 g (0.1 mole) of sodium thiosulfate pentahydrate in 30 ml of H_2O was heated on a steam bath *ca.* 0.5 hr. The product, which was separated from the cooled solution, was recrystallized from H_2O and washed with hot MeOH until halide free to give 11.5 g (62%) of white crystals, mp 208–209° dec (lit.[14] mp 206° dec). *Anal.* ($C_4H_{11}NO_3S_2$) C, H, N, S.

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(12) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, N. J. 08840, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. 11377. Infrared spectra were determined as KBr pellets on a Beckman IR-5 spectrophotometer.

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Terpene Compounds as Drugs. VI. Acyclic Mono- and Sesquiterpene Thiocyanates and Isothiocyanates

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Many aliphatic and aromatic thiocyanates and isothiocyanates, especially the allyl and benzyl derivatives, are endowed with interesting antimicrobial properties.[1] This, together with our interest in the terpene field, has led us to synthesize esters of thiocyanic and isothiocyanic acid with terpene alcohols such as citronellol, geraniol, and farnesol.

Citronellyl (II), geranyl (IV), and farnesyl isothiocyanate (VI) were obtained from the proper amines by reaction with CS_2 and $ClCOOC_2H_5$. Thiocyanates were obtained by treating terpenyl bromides with NaSCN. Citronellyl bromide gave the related thiocyanate (I); geranyl bromide yielded linalyl isothiocyanate together with geranyl thiocyanate (III); farnesyl bromide yielded nerolidyl isothiocyanate together with farnesyl thiocyanate (V).

The structure of all the compounds and the composition of III and V were determined by pmr. Our values were in good agreement with those reported for similar compounds.[2] Integration of the linalyl olefinic protons and CH_2SCN methylene protons gave 80.56% of linalyl isothiocyanate and 19.44% of geranyl thiocyanate for III. A similar assay gave 83.34% of nerolidyl isothiocyanate and 16.66% of farnesyl thiocyanate for V. Since these data were taken in CCl_4 solution at 36° and an equilibrium is involved, it may be expected that changes in the experimental conditions give different percentage compositions of III and V.

Table I reports the new products, along with yields and analytical data.

TABLE I

PHYSICOCHEMICAL PROPERTIES OF ACYCLIC TERPENE THIOCYANATES AND ISOTHIOCYANATES

Compd	Yield, %	Bp, °C (mm)	n_D (25°)	R_f (tlc)	Formula[a]
I	44	79–80 (0.15)	1.4832	0.48	$C_{11}H_{19}NS$
II	45	81–82 (0.2)	1.5021	0.74	$C_{11}H_{19}NS$
III	57	62–64 (0.1)	1.5061	0.47, 0.81	$C_{11}H_{17}NS$
IV	43	81–82 (0.15)	1.5221	0.76	$C_{11}H_{17}NS$
V	45	115–116 (0.22)	1.4893	0.48, 0.83	$C_{16}H_{25}NS$
VI	53	125–127 (0.2)	1.5206	0.77	$C_{16}H_{25}NS$

[a] All compounds were analyzed for C, H, N, S; the analytical values were within ±0.4% of the theoretical values.

Biological Results.—*Micrococcus pyogenes var. aureus* (ATCC 6538 P), *Bacillus subtilis* (ATCC 6633), *Escherichia coli* Mc. Leod (ATCC 10536), *Salmonella typhi* (T 30 Roma), *Candida albicans* (DM), *Trichomonas foetus*, and *Entamoeba histolytica* (F 22) were used as test organisms. Minimum inhibitory concentrations required to prevent growth of bacteria for 24 hr at 37° were determined by serial dilution in tryptose phosphate broth (Difco). The *in vitro* activity against *T. foetus* was determined by serial dilution in fluid thioglycolate medium (Difco) with 10% horse serum added; test tubes containing 5 ml of the liquid media were inoculated with 40,000–70,000 parasites/ml; minimum inhibitory concentrations were determined microscopically after 48 hr of standing at 37°. The antiamebic activity *in vitro* was determined according to De Carneri.[3]

In none of the assays did the compounds exert any observable inhibitory activity even at a concentration level of 400 μg/ml. In contrast, the standard allyl and benzyl isothiocyanate confirmed their good activity.

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Experimental Section[4]

Citronellyl Thiocyanate (I).—Citronellyl bromide (9 g, 0.041 mole) was added during 0.5 hr, with stirring at room temperature, to a solution of NaSCN (3.33 g, 0.041 mole) in anhydrous EtOH (50 ml). The mixture was then refluxed for 3 hr, cooled, filtered, and evaporated. The residue was taken up in Et_2O to remove the salts. Evaporation of the Et_2O solution gave an oil which was distilled *in vacuo* under N_2 to yield 3.6 g of I as a colorless oil: ν_{max} 2158 cm^{-1} (SC≡N, sharp); pmr, δ 0.96 (doublet, $>CCH_3$), 1.61 (singlet, CCH_3=CH(CH_2)$_2$-*trans* CH_3), 1.68 (singlet, CCH_3=CH(CH_2)$_2$-*cis* CH_3), 2.95 (triplet, α-CH_2), and 5.06 (triplet, -CH=).

Citronellyl Isothiocyanate (II).—Citronellylamine (9.31 g, 0.06 mole) was added dropwise during 0.5 hr, with stirring at 10–15°, to CS_2 (4.56 g, 0.06 mole) and NaOH (2.4 g, 0.06 mole) in H_2O (25 ml). After refluxing for 2 hr and cooling to 35–40°, $ClCOOC_2H_5$ (6.51 g, 0.06 mole) was dropped into the mixture during 1 hr, taking care that the temperature did not exceed internal 40°. After an additional 0.5 hr of stirring, the separated oil was extracted (Et_2O), and the extract was washed (4% $NaHCO_3$, H_2O), dried (Na_2SO_4), and evaporated. The residue was distilled at 87–92° (0.5 mm) to yield 5.28 g of II as a colorless oil: ν_{max} 2121 cm^{-1} (N=C=S, broad); pmr, δ 0.96 (doublet, $>CCH_3$), 1.61 (singlet, CCH_3=CH(CH_2)$_2$-*trans* CH_3), 1.68 (singlet, CCH_3=CH(CH_2)$_2$-*cis* CH_3), 3.55 (triplet, α-CH_2), and 5.06 (triplet, -CH=).

Geranyl isothiocyanate (IV) was prepared as was II; ν_{max} 2101 cm^{-1} (N=C=S, broad); pmr, δ 1.61 (singlet, CCH_3=CH(CH_2)$_2$-*trans* CH_3), 1.69 (singlet, CCH_3=CH(CH_2)$_2$-*cis* CH_3 and CCH_3=$CHCH_2NCS$ CH_3), 4.06 (doublet, α-CH_2), 5.06 (triplet, CCH_3=$CH(CH_2)_2$ olefinic proton), and 5.37 (triplet, CCH_3=$CHCH_2NCS$ olefinic proton).

Farnesyl isothiocyanate (VI) was prepared as was II; ν_{max} 2101 cm^{-1} (N=C=S, broad); pmr, δ 1.60 (singlet, CCH_3=CH(CH_2)$_2$-*trans* CH_3), 1.68 (singlet, CCH_3=CH(CH_2)$_2$-*cis* CH_3 and CCH_3=$CHCH_2NCS$ CH_3), 4.06 (doublet, α-CH_2), 5.06 (triplet, CCH_3=$CH(CH_2)_2$ olefinic protons), and 5.37 (triplet, CCH_3=$CHCH_2NCS$ olefinic proton).

Linalyl Isothiocyanate and Geranyl Thiocyanate (III).—Geranyl bromide (10.85 g, 0.05 mole) was added dropwise during 15 min, with stirring at 0°, to a solution of NaSCN (4.05 g, 0.05 mole) in anhydrous EtOH (50 ml). After an additional 0.5 hr of stirring at room temperature, the suspension was filtered and the solution was evaporated. The residue was taken up in Et_2O, washed (H_2O), dried (Na_2SO_4), and evaporated. The new residue was distilled at 68–73° (0.15 mm) to yield 5.55 g of a colorless oil (III), which consisted (by pmr) of linalyl isothiocyanate (80.56%) and geranyl thiocyanate (19.44%): ν_{max} 2090 (N=C=S and SC≡N, broad) and 984 and 925 cm^{-1} (vinyl =CH bonds); pmr, δ 1.47 (singlet, $>CCH_3$), 1.61 (singlet, CCH_3=CH(CH_2)$_2$-*trans* CH_3), 1.68 (singlet, CCH_3=CH(CH_2)$_2$-*cis* CH_3 and CCH_3=$CHCH_2SCN$ CH_3), 3.62 (doublet, α-CH_2), 5.06 (triplet, CCH_3=$CH(CH_2)_2$ olefinic protons), and 5.39 (triplet, CCH_3=$CHCH_2SCN$ olefinic proton).

Nerolidyl Isothiocyanate and Farnesyl Thiocyanate (V).—Reaction of farnesyl bromide with NaSCN, carried out as was described for III, yielded a colorless oil (V), which consisted (by pmr) of nerolidyl isothiocyanate (83.34%) and farnesyl thiocyanate (16.66%): ν_{max} 2084 (N=C=S and SC≡N, broad) and 984 and 925 cm^{-1} (vinyl =CH bonds); pmr, δ 1.48 (singlet, $>CCH_3$), 1.60 (singlet, CCH_3=CH(CH_2)$_2$-*trans* CH_3), 1.68 (singlet, CCH_3=CH(CH_2)$_2$-*cis* CH_3 and CCH_3=$CHCH_2SCN$ CH_3), 3.62 (doublet, α-CH_2), 5.06 (triplet, CCH_3=$CH(CH_2)_2$ olefinic protons), and 5.39 (triplet, CCH_3=$CHCH_2SCN$ olefinic proton).

(4) Boiling points are uncorrected. The R_f values were determined on glass chromatostrips coated with silica gel GF_{254} Merck; the tlc was performed with cyclohexane–ethyl acetate (95:5). The spots were detected with a 1% solution of vanillin in concentrated H_2SO_4. Ir spectra were recorded between rock salt plates with a Perkin-Elmer grating spectrophotometer Model 337. Pmr spectra were taken with a Varian spectrometer Model A-60 A operating at 60.00 Mc, in a radiofrequency range of 0.02–0.04 mG (sample temperature, 36°). The reference zero standard was internal Me_4Si and the chemical shifts are given in parts per million downfield from this point (δ scale).

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New Compounds

The Synthesis of Certain 3,5-Dimethyl-N¹-arylsulfonylpyrazoles and 3-Methyl-N¹-arylsulfonyl-5-pyrazolones

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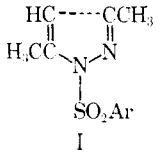
Pyrazole and 5-pyrazolone derivatives present a variety of pharmacological applications, especially the hypoglycemic activity of several pyrazoles[1-3] and the antidiuretic effects of 5-pyrazolones.[4,5] We now report the preparation of certain 3,5-dimethyl-N¹-arylsulfonylpyrazoles (I) (Table I) and 3-methyl-N¹-arylsulfonyl-5-pyrazolones (III) (Table III) from the corresponding 1-arylsulfonylhydrazides.[6]

TABLE I



I

Ar	Mp, °C[a]	Yield, %[b]	Method	Formula[c]	Analyses
p-$C_2H_5OC_6H_4$	103–105	64.4	A	$C_{13}H_{16}N_2O_3S$	C, H, N
p-*n*-$C_3H_7OC_6H_4$	45–46	31.8	B	$C_{14}H_{18}N_2O_3S$	C, H, N
$C_6H_5CH_2$	76–77	73.5	A	$C_{12}H_{14}N_2O_2S$	C, H, N

[a] The melting points were determined in open capillary tubes and are uncorrected. [b] The yields are based on the product of the first recrystallization. [c] All analytical results were within ±0.3% of the theoretical values.

Experimental Section

3,5-Dimethyl-N¹-arylsulfonylpyrazoles (I) (Table I). Method A.—To a solution of 0.002 mole of the 1-arylsulfonyl hydrazide in

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