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, -C*H*=).

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, -C*H*=).

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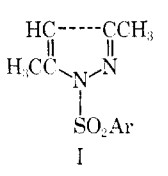
Pyrazole and 5-pyrazolone derivatives present a variety of pharmacological applications, especially the hypoglycemic activity of several pyrazoles[1–3] and the antidiuretic effects of 5-pyrazolones.[4,5] We now report the preparation of certain 3,5-dimethyl-N¹-arylsulfonylpyrazoles (I) (Table I) and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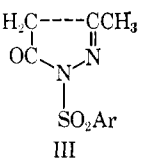
TABLE II

$CH_3CCH_2CO_2C_2H_5$
$\|$
$NNHSO_2Ar$
II

Ar	Mp, °C[a]	Yield, %[b]	Method	Formula[c]	Analyses
p-$CH_3OC_6H_4$	110–111	65.8	C	$C_{13}H_{18}N_2O_5S$	C, H, N
p-$C_2H_5OC_6H_4$	106–107	55.8	C	$C_{14}H_{20}N_2O_5S$	C, H, N
$C_6H_5CH_2$	79–80	52.7	D	$C_{13}H_{18}N_2O_4S$	N

[a–c] See footnotes *a–c* in Table I.

TABLE III



III

Ar	Mp, °C dec[a]	Yield, %[b]	Formula[c]	Analyses
p-$CH_3OC_6H_4$	137–138	34.5	$C_{11}H_{12}N_2O_4S$	C, H, N
p-$C_2H_5OC_6H_4$	168	44.6	$C_{12}H_{14}N_2O_4S$	C, H
$C_6H_5CH_2$	120–122	40.1	$C_{11}H_{12}N_2O_3S$	C, H, N

[a–c] See footnotes *a–c* in Table I.

50 ml of 95% EtOH, 0.004 mole of acetylacetone was added. The solution was refluxed 1–2 hr, then left overnight at 3°. Recrystallization from MeOH gave white crystals.

Method B.—Equimolar quantities of acetylacetone and the 1-arylsulfonylhydrazide (0.002 mole), were dissolved in 30 ml of DMF at 0°, and 3 drops of 2 *N* HCl were added. The solution was stirred at room temperature for 2 hr, then left at 3° overnight. The transparent white crystals thus obtained were recrystallized from 1:1 Et_2O–petroleum ether (40–60°).

1-Arylsulfonylhydrazones of Ethyl Acetoacetate (II) (Table II). Method C.—To a solution of 0.002 mole of the 1-arylsulfonylhydrazide in 50 ml of 95% EtOH, was added 0.004 mole of ethyl acetoacetate. The solution was refluxed 1–2 hr, then left overnight at 3°. The white crystals were filtered and recrystallized from EtOH.

Method D.—Equimolar quantities (0.002 mole) of ethyl acetoacetate and the 1-arylsulfonylhydrazide were dissolved in 50 ml of 95% EtOH, and 2 ml of 5% AcOH was added. The solution was stirred at room temperature for 2 hr, then left overnight at 3°. The white crystals were filtered and recrystallized from 1:1 MeOH–H_2O.

3-Methyl-N¹-arylsulfonyl-5-pyrazolones (III) (Table III).—The 1-arylsulfonylhydrazone of ethyl acetoacetate (0.002 mole) was dissolved in 10 ml of 5% Na_2CO_3 and held at 80–90° for 2–3 hr. It was then cooled and brought to pH 3 with 0.6 *N* HCl, then left overnight at 3°. The white powder obtained was recrystallized from H_2O.

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Preparation of (Carboxymethyl)cyclohexyldimethylammonium Chloride Hydrazide

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In studies of the reaction of cationic hydrazides with carbonyl groups in periodate-oxidized starches[1,2] we synthesized (carboxymethyl)cyclohexyldimethylammonium chloride hydrazide by the method of Girard and Sandulesco[3] for Girard T reagent. The new compound might be of value in isolating ketones from steroid mixtures[3] and aldehydes from autoxidized fats and oils.[4]

(1) C. L. Mehltretter, T. E. Yeates, G. E. Hamerstrand, B. T. Hofreiter, and C. E. Rist, *Tappi*, **45**, 750 (1962).

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Experimental Section

(Carboxymethyl)cyclohexyldimethylammonium Chloride Hydrazide.—N,N-Dimethylcyclohexylamine[5] (53.4 g, 0.42 mole) was added dropwise to a stirred solution of ethyl chloroacetate (49.0 g, 0.40 mole) in 100 ml of absolute EtOH at 5°. The mixture was stirred at 5–10° for 30 min, then heated at 60–70° for 1 hr, and allowed to stand at room temperature overnight to form the intermediate ethyl ester of (carboxymethyl)cyclohexyldimethylammonium chloride in solution.

Hydrazine of 95+% purity (13.5 g, 0.40 mole) was added dropwise to this solution during 15 min of continuous stirring with the temperature rising to 50–60°. The reaction mixture was maintained at this temperature range for 1 hr and then concentrated *in vacuo* to about 100 ml. When an equal volume of EtOAc was added to the concentrate and it was kept at 2° for 36 hr, crystallization occurred. The extremely hygroscopic product was filtered off in an atmosphere of 11% relative humidity and dried *in vacuo* over P_2O_5. Recrystallization from EtOAc–EtOH (5:1) gave 57.6 g (61%) of the hydrazide, mp 160–164°. *Anal.* ($C_{10}H_{22}ClN_3O$) C, H, N, Cl.

Acknowledgments.—We thank Mrs. Clara McGrew and Mrs. Bonita Heaton for the microanalyses.

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3,3-Disubstituted Ethyl Carbazates[1]

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The antitumor activity of such hydrazine derivatives as MIH [$CH_3NHNHCH_2C_6H_4CONHCH(CH_3)_2$], 1-acetyl-2-picolinoylhydrazide, and 5-(3,3-dimethyl-1-triazeno)-4-imidazolecarboxamide, has encouraged us to prepare some 3,3-disubstituted ethyl carbazates for screening.

The lack of significant activity (Table I) in those compounds (**1–4**) which are not alkylating agents would seem to indicate that the activity of **5** is related to its alkylating properties rather than to any properties it may have as a substituted hydrazine.

Experimental Section[2]

Ethyl 3,3-Bis(chloroallyl)carbazates.—Compounds **1–4** were prepared from the appropriate dichloroalkene (0.5 mole), ethyl carbazate[3] (0.25 mole), and NaOH (0.5 mole) in absolute EtOH (50 ml). The mixture was shaken with cooling for 1 hr, followed by shaking for an additional 8 hr, then filtered. The filtrate was

(1) This work was supported by Research Grant CA-06586 from the National Cancer Institute, National Institutes of Health, to the University of Kentucky Research Foundation.

(2) Melting points were taken on a Fisher-Johns melting point block and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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