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SULFUR-CONTAINING SPIROCYCLIC COMPOUNDS BASED ON 3-METHYL-(AMINO)-1-PHENYLPYRAZOL-5-ONES

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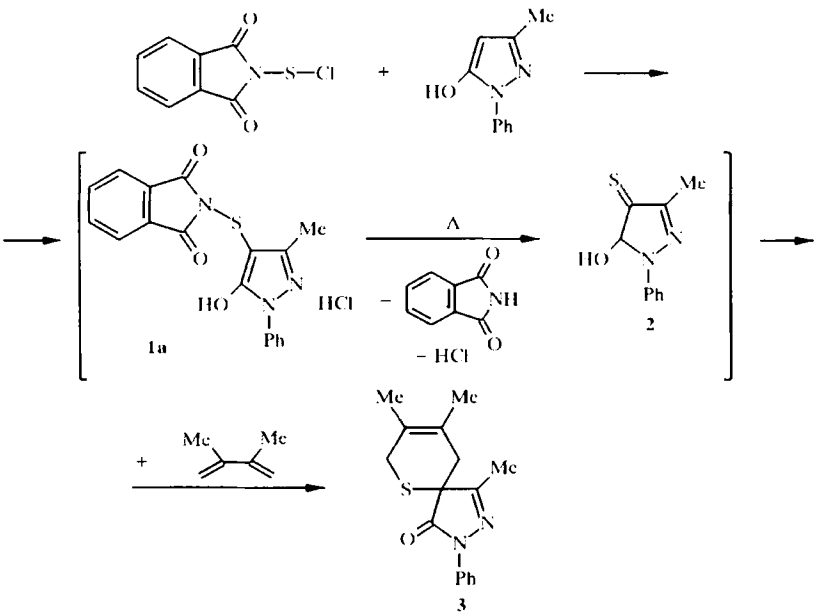
3-Methyl(amino)-1-phenylpyrazol-5-ones react with N-chlorosulfenylphthalimide to give 4-phthalimidothiopyrazoles which decompose to form 3-methyl(amino)-1-phenylpyrazol-5-one-4-thiones. They were identified as their spirocyclic adducts with dienes. Oxidation of the latter with m-chloroperbenzoic acid gives spirocyclic sulfoxides and sulfones.

Keywords: spiro[(1-phenylpyrazol-5-one)-4-thiane], 1-phenylpyrazol-5-one, N-chlorosulfenylphthalimide.

We have previously reported [1] the reaction of N-chlorosulfenylphthalimide with 3-methyl-1-phenyl-5-substituted pyrazoles to give 4-phthalimidothiopyrazoles. Thermal decomposition of hydrochloride of 5-hydroxy-3-methyl-1-phenyl-4-phthalimidothiopyrazole (**1a**) leads to 3-methyl-1-phenylpyrazol-5-one-4-thione (**2**) which was isolated as butadiene cycloadduct (**3**) in 58% yield [1] (scheme 1).

Scheme 1



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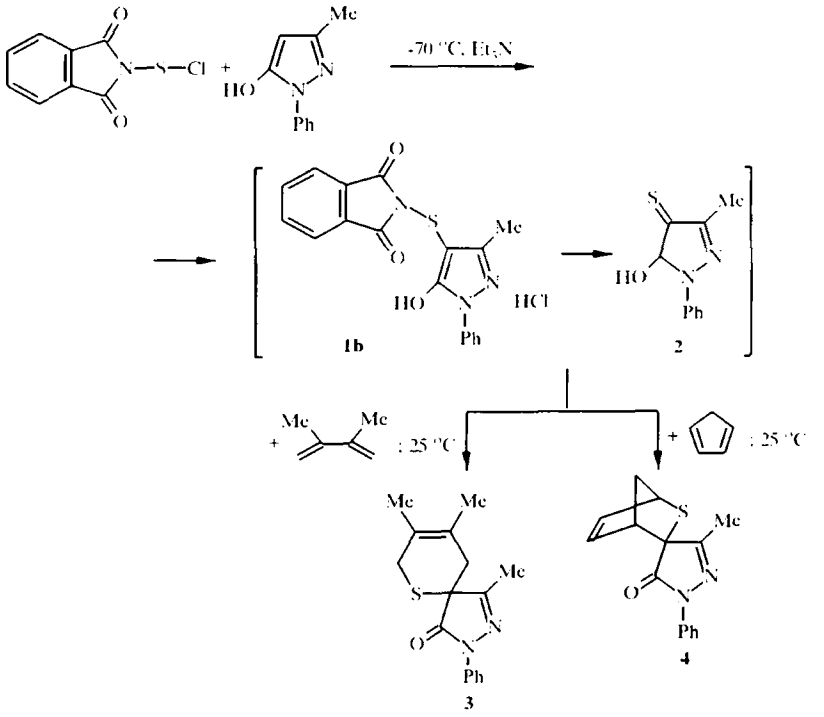
Compounds which contain α-oxothioketone fragment are unknown in the pyrazole series. Bearing in mind the high activity of the thiocarbonyl group of compound **2** in cycloaddition reaction we have investigated in detail the synthesis of 4-phthalimidothiopyrazole **1a** (and its analog containing amino group in position 3) together with the reaction of pyrazol-5-one-4-thiones with dienes and the chemical properties of the compounds formed in this way.

If 4-phthalimidothiopyrazole **1a** is formed by mixing N-chlorosulfenylphthalimide with 3-methyl-1-phenylpyrazol-5-one at 20°C in benzene solution in the absence of HCl acceptor, then the formation of the pyrazole base (**1b**) occurs under milder conditions (i.e. by treating N-chlorosulfenylphthalimide with 3-methyl-1-phenylpyrazol-5-one at -70°C in dichloromethane in the presence of triethylamine). 4-Phthalimidopyrazole **1b** is stable for several hours in this solution at 20-25°C but it could not be isolated in pure state; when dichloromethane is removed in vacuo at 0°C the compound decomposes. The residue obtained contained phthalimide and a mixture of unidentified substances. The optimum is apparently use of pyrazole **1b** for further reactions as a freshly prepared solution in dichloromethane at a temperature not greater than 25°C. For conversion of compound **1b** to the pyrazol-5-one-4-thione **2** we have used the reaction with pyridine [2]. In this way, phthalimide splits off to give a dark blue solution of the compound and subsequent addition of cyclopentadiene gives product **4** in 34% yield. The yield of the cycloadducts **3** and **4** is increased to 79-82% by the addition of pyridine to the solution of pyrazole **1a** in the presence of diene (scheme 2).

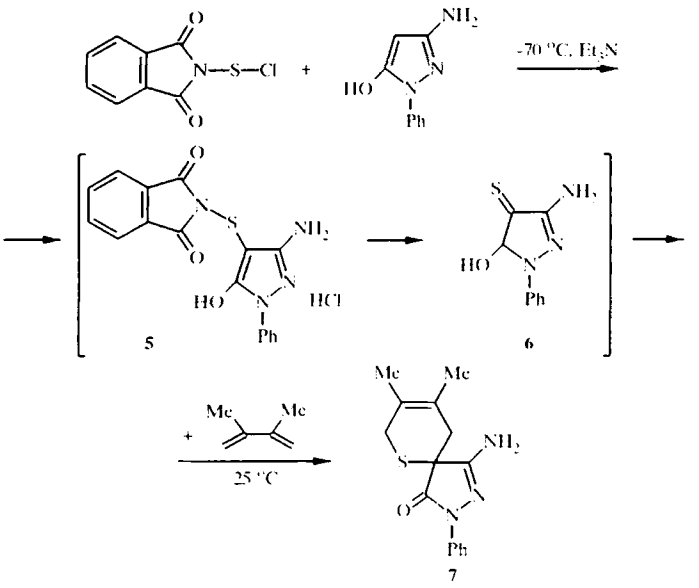
Scheme 2



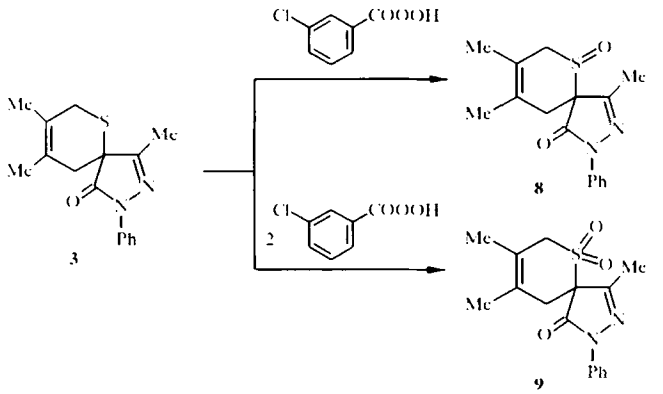
The spirocyclic compound **7** was obtained in a similar way from 3-amino-1-phenylpyrazol-5-one. The stability of 4-phthalimidothiopyrazole **5** is evidently lower than that of **1b**. As judged by the appearance of phthalimide precipitate, decomposition of compound **5** occurs at once as soon as the temperature of the reaction mixture reaches 20°C without the addition of pyridine (scheme 3).

The spirocyclic compounds **3**, **4**, and **7**, which contain thiane fragment at position 4 of the pyrazole ring, are a novel type of pyrazolones. The sulfur atom in these compounds is readily oxidized by *m*-chloroperbenzoic acid. Hence compound **3** can give sulfoxides **8** or sulfones **9** depending on the proportions of reagents (scheme 4).

Scheme 3



Scheme 4



The molecule of sulfoxide **8** has two asymmetric centers, hence formation of a pair of diastereomers might be expected. The ^{1}H NMR spectrum of sulfoxide **8**, isolated in 20% yield, shows two sets of signals corresponding to 91: 9 ratio of these isomers and points to the high diastereoselectivity of the oxidation reaction. The low-field shift of the ^{1}H NMR spectroscopic signals for the CH_3 group protons in the pyrazole ring of sulfoxide **8** ($\Delta\delta$ = 0.23 ppm) and sulfone **9** ($\Delta\delta$ = 0.26 ppm) when compared with the starting compound **3** merits attention. A similar ^{1}H NMR spectroscopic low-field shift was also observed for signals of protons of the CH_3 group in position 3 in the pyrazole ring of sulfone **11** ($\Delta\delta$ = 0.25 ppm), which was prepared by oxidation of 5-hydroxy-3-methyl-4-(*p*-nitrophenylthio)-1-phenylpyrazole **10** [3] (scheme 5).

Scheme 5

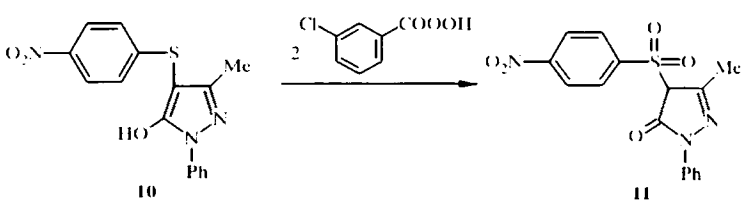


TABLE 1. Characheristics of the Compounds Synthesized

Compound	Empirical formula	Found, % Calculated, %		mp, °C	Yield, %
		N	S		
3	$C_{16}H_{18}N_2OS$	9.80 9.78	11.25 11.20	83–85	82
4*	$C_{15}H_{18}N_2OS$	10.43 10.36	12.05 11.86	92–100	79
7	$C_{15}H_{17}N_3OS$	14.60 14.62	10.89 11.16	140–142	61
8*[2]	$C_{16}H_{18}N_2O_2S$	9.30 9.26	10.88 10.60	136–138	20
9	$C_{16}H_{18}N_2O_2S$	9.05 8.80	10.37 10.07	183–185	63
11	$C_{16}H_{18}N_2O_2S$	11.63 11.69	9.18 8.92	198–200	72

* Ratio of diastereomers 81: 19

*[2] Ratio of diastereomers 91: 9

This kind of shift infers a significant interaction through space between the SO or SO_2 fragment and the CH_3 group. Quantum-chemical calculations of two of the possible structures for the sulfoxide **8** were carried out by the SCF MO LCAO method in the MNDO semi-empirical approximation with PM3 parameterization [4, 5] and have shown that the structure of spiro[(3-methyl-1-phenylpyrazol-5-one)-4(*S*),6'-(3',4'-dimethyl-1'(*S*)-oxo-6'H-2',5'-dihydrothiane)] (**8a**), in which the oxygen atom of the sulfoxide group and the CH_3 group approach one another and are sited over the plane of the thiane ring, has enthalpy of formation of 8.783 kcal/mole. By contrast, the structure of spiro[(3-methyl-1-phenylpyrazol-5-one)-4(*R*),6'-(3',4'-dimethyl-1'(*S*)-oxo-6'H-2',5'-dihydrothiane)] (**8b**) has a different arrangement of the SO and CH_3 groups relative to the thiane ring and is energetically less favored (enthalpy of formation 27.842 kcal/mole).

TABLE 2. Spectral Characheristics of the Compounds Synthesized

Compound	^{1}H NMR spectrum, ppm (*J*, Hz)	IR spectrum, cm^{-1}
3	DMSO-d_6: 1.75 (s), 1.67 (s) (6H, $2CH_3$); 2.05 (3H, s, CH_3); 2.29, 2.54 (2H, CH_2, J_{AB} = 17.1); 3.16, 3.56 (2H, CH_2, J_{AB} = 16.5); 7.16 (1H, t, arom.); 7.39 (2H, t, arom.); 7.77 (2H, d, arom.)	3090, 2550, 1635, 1600
4	C_6D_6: 1.63 (3H, s, CH_3); 1.13, 2.99 (2H, CH_2, J_{AB} = 9.6); 2.81 (1H, s, CH); 3.62 (1H, s, CH); 5.29 (1H, dd, CH); 6.00 (1H, dd, CH); 6.96 (1H, t, arom.); 7.23 (2H, t, arom.); 8.38 (2H, d, arom.); Second diastereomer, 19%: 1.86 (3H, s, CH_3); 1.55, 1.94 (2H, CH_2, J_{AB} = 9.3); 2.69 (1H, s, CH); 3.68 (1H, s, CH); 6.11 (1H, dd, CH); 6.38 (1H, dd, CH); 6.94-8.32 (5H, arom.)	3050, 2985, 2950, 1710, 1620, 1600
7	$CDCl_3$: 1.81 (s), 1.88 (s) (6H, $2CH_3$); 2.48, 2.60 (2H, CH_2, J_{AB} = 16.3); 3.16, 3.65 (2H, CH_2, J_{AB} = 15.6); 4.52 (2H, s, NH_2); 7.13 (1H, t, arom.); 7.37 (2H, t, arom.); 7.90 (2H, d, arom.)	3415, 3360, 3270, 3210, 2925, 2900, 2875, 2830, 1695, 1660, 1600
8	DMSO-d_6: 1.65 (s), 1.76 (s) (6H, $2CH_3$); 2.28 (3H, s, CH_3); 2.66, 2.82 (2H, CH_2, J_{AB} = 18.6); 3.81, 4.16 (2H, CH_2, J_{AB} = 14.8); 7.22 (1H, t, arom.); 7.44 (2H, t, arom.); 7.81 (2H, d, arom.); $CDCl_3$: 1.71 (s), 1.83 (s) (6H, $2CH_3$); 2.33 (3H, s, CH_3); 2.55, 2.70 (2H, CH_2, J_{AB} = 18.6); 3.55, 4.52 (2H, CH_2, J_{AB} = 15.0); 7.18 (1H, t, arom.); 7.38 (2H, t, arom.); 7.90 (2H, d, arom.); Second diastereomer, 9%: 3.34, 3.95 (CH_2, J_{AB} = 16.5)	3090, 3010, 2955, 2925, 2880, 1710, 1605
9	DMSO-d_6: 1.71 (s), 1.75 (s) (6H, $2CH_3$); 2.31 (3H, s, CH_3); 2.92, 3.14 (2H, CH_2, J_{AB} = 18.0); 3.86, 4.21 (2H, CH_2, J_{AB} = 17.1); 7.26 (1H, t, arom.); 7.46 (2H, t, arom.); 7.79 (2H, d, arom.)	2960, 2930, 1718, 1605
11	DMSO-d_6: 2.40 (3H, s, CH_3); 7.29 (1H, t, arom.); 7.45 (2H, t, arom.); 7.62 (2H, d, arom.); 8.23 (2H, d arom.); 8.40 (2H, d, arom.)	3120, 2550, 1635, 1600, 1540, 1380

EXPERIMENTAL

IR spectra were recorded on an UR-10 instrument for KBr tablets and ^{1}H NMR spectra were obtained on a Varian VXR (300 MHz) instrument using TMS as internal standard. Reaction monitoring was carried out using Silufol UV-254 plates with $CHCl_3$–MeOH (9:1) as eluent.

Parameters for the compounds prepared are given in Tables 1 and 2.

Spiro[(3-methyl-1-phenylpyrazol-5-one)-4,6'-(3',4'-dimethyl-6'H-2',5'-dihydrothiane)] (3), Spiro[(3-methyl-1-phenylpyrazol-5-one)-4,3'-(2'-thiabicyclo[2.2.1]hept-5-ene)] (4), and Spiro[(3-amino-1-phenylpyrazol-5-one)-4,6'-(3',4'-dimethyl-6'H-2',5'-dihydrothiane)] (7). Mixture of 3-methyl-1-phenylpyrazol-5-one or 3-amino-1-phenylpyrazol-5-one (5.91 mmol) and triethylamine (5.91 mmol) was added dropwise with stirring and cooling to -70°C over 30 min to solution of N-chlorosulfenylphthalimide (6.50 mmol) in dichloromethane (20 ml). The reaction mixture was heated to 0-2°C over 40 min and 2,3-dimethylbutadiene (11.81 mmol) was added for the preparation of compounds **3** and **7** or cyclopentadiene (11.81 mmol) was added for preparation of compound **4**. The product was then heated to 20°C and pyridine (17.73 mmol) was added. After 24 h the precipitated phthalimide was filtered off and the reaction solution was evaporated in vacuo (20 mm Hg). For preparation of compounds **3** and **4**, the residue was extracted with *n*-hexane (6 × 10 ml) and this solution crystallized to give compounds **3** or **4** on cooling. For compound **7**, the residue was washed with water (50 ml), dissolved in chloroform (15 ml), the insoluble phthalimide was filtered off, and the solvent was evaporated in vacuo (20 mm Hg). Compound **7** was recrystallized from benzene.

Spiro[(3-methyl-1-phenylpyrazol-5-one)-4,6'-(3',4'-dimethyl-1'-oxo-6',H-2',5'-dihydrothiane)] (8). To solution of compound **3** (1.75 mmol) in chloroform (7 ml) solution of equimolar amount of *m*-chloroperbenzoic acid in chloroform (7 ml) was added under stirring. After 24 h, the solvent was evaporated in vacuo (20 mm Hg). The product was recrystallized from ethanol (3 ml).

Spiro[(3-methyl-1-phenylpyrazol-5-one)-4,6'-(3',4'-dimethyl-1',1-dioxo-6'H-2',5'-dihydrothiane)] (9) and 5-Hydroxy-3-methyl-4-(*p*-nitrophenylsulfo)-1-phenylpyrazole (11). To suspension of compound **3** or **10** (1.75 mmol) in ethanol (7 ml) *m*-chloroperbenzoic acid (3.50 mmol) was added under stirring. After 5 h, compounds **9** or **11** were filtered off and purified by recrystallization from ethanol.

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