REACTION OF 2-METHYL-3-ETHOXYCARBONYL-4-HYDROXYTHIOPHENE WITH HYDRAZINES

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2-Methyl-3-ethoxycarbonyl-4-(N,N-dimethylhydrazino)thiophene (II) and 2-methyl-3-ethoxy-carbonyl-4-(N-phenylhydrazino)thiophene (III) are formed by the action of substituted hydrazines — N,N-dimethylhydrazine and phenylhydrazine — on 2-methyl-3-ethoxycarbonyl-4-hydroxythiophene (I). At the same time, the thiophene ring of hydroxythiophene I undergoes hydrazinolysis under the influence of hydrazine hydrate to form 3-mercaptomethyl-4-ethoxycarbonyl-5-methylpyrazole (IV). Structure IV was proved by IR, UV, and PMR spectroscopy and by hydrogenolysis of IV to the known 3,5-dimethyl-4-ethoxycarbonylpyrazole (V).

Continuing our study of the properties of 2-methyl-3-ethoxycarbonyl-4-hydroxythiophene (I), we have found that 2-methyl-3-ethoxycarbonyl-4-(N,N-dimethylhydrazino)thiophene (II) is obtained when I is heated with N,N-dimethylhydrazine acetate. As demonstrated by Benary and Baravian [1] and confirmed by us on the basis of spectral data, 2-methyl-3-ethoxycarbonyl-4-(N-phenylhydrazino)thiophene (III) is formed by the reaction of hydroxythiophene I with phenylhydrazine. The UV spectrum of II contains two absorption maxima characteristic for thiophene derivatives [2] at 230 nm (log ε 4.58) and 315 nm (log ε 3.35). A certain bathochromic shift of the absorption band from 315 to 329 nm (log ε 3.44) and the appearance of a new absorption maximum at 290 nm (log ε 4.40) are observed in the UV spectrum of III; no definite change in the position of the maximum at 230 nm was observed. These results are in agreement with the spectral characteristics of arylaminothiophenes [3].

A singlet at 6.06 ppm, which can be assigned to the proton in the α-position of the thiophene ring, and a weak signal from the NH proton at 6.31 ppm [3] are noted in the PMR spectrum of II. In the spectrum of III, the signal of the α proton of the thiophene ring is shifted somewhat to stronger field (5.90 ppm), while the signals of the NH protons appear as broad singlets at 5.58 and 7.58 ppm.

In order to synthesize 2-methyl-3-ethoxycarbonyl-4-hydrazinothiophene, the thiophene analog of the substituted phenylhydrazine [4], we made a detailed study of the reaction of hydroxythiophene I with hydrazine hydrate. We found that this reaction proceeds anomalously and, as a result of hydrazinolysis, leads to 3-mercaptomethyl-4-ethoxycarbonyl-5-methylpyrazole (IV). Compound IV is formed by the action of hydrazine hydrate at both low temperatures and on heating. The IV structure was proved by IR, UV, and PMR spectroscopy and by its conversion to the known 3,5-dimethyl-4-ethoxycarbonylpyrazole (V) by hydrogenolysis over Raney nickel [5].

A distinct but rather weak band of the valence vibrations of the mercapto group is observed at 2560 cm^{-1} in the IR spectrum of mercaptomethylpyrazole IV; this band vanishes in the spectrum of 3-(2',4'-dinitrophenyl)thiomethyl-4-ethoxycarbonyl-5-methylpyrazole (VI). The UV spectrum of IV contains only one absorption maximum at 226 nm (log ε 4.01), i.e., in the region of pyrazole absorption [6]. The following signals are noted in the PMR spectrum of mercaptomethylpyrazole IV: that of an ethyl group at δ 4.35 ppm (CH$_2$, quartet, two proton units), of the methyl group at 2.50 ppm (singlet, three proton units), and two broad singlets at 2.16 ppm (one proton unit) and 3.95 ppm (two proton units). The last two signals of the spectrum can apparently be assigned to the protons of the two adjacent SH and CH$_2$ groups. This sort of broadening

II R=R'=CH₃; III R=H, R'=C₆H₅
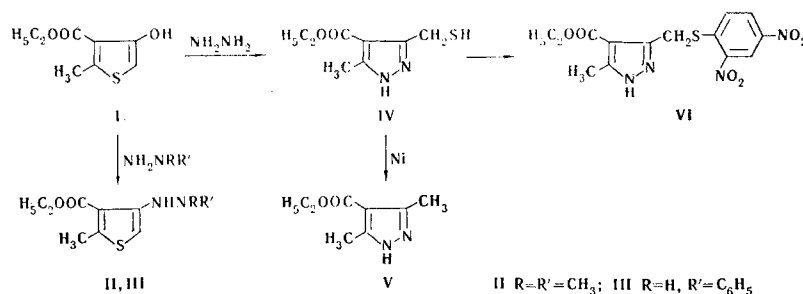
of the signals occurs because of the presence of rather rapid intermolecular and intramolecular chemical exchange of the SH proton. When the temperature is lowered, one should expect retardation of this proton exchange, which ought to induce a change in the form of the signals because of spin–spin interaction of the protons of the CH_2 and SH groups. In fact, a triplet at 2.30 ppm (1 proton unit) and a doublet at 3.95 ppm (2 proton units) with an overall spin–spin interaction constant of 8 Hz appear in the spectrum recorded at −30°. The first signal should be assigned to the SH proton, while the second should be assigned to the protons of the CH_2 group. For labile protons of the SH type it is natural to expect a shift in the signal to weak field with decreasing temperature; this is observed in this case (2.16 ppm at 20° and 2.30 ppm at −30°). A signal corresponding to the NH proton of the pyrazole ring [7] is not observed. The signal of the NH proton is markedly broadened and merges with the zero line, probably because of rapid exchange with the SH and NH groups of other molecules.

There is no information in the literature regarding the hydrazinolysis of thiophene derivatives. We first observed this reaction in the thiophene series in the case of 2-methyl-3-ethoxycarbonyl-4-hydroxy-thiophene, while such transformations are common for several other heterocyclic systems [8-12].

EXPERIMENTAL

2-Methyl-3-ethoxycarbonyl-4-(N,N-dimethylhydrazino)thiophene (II). A mixture of 3.7 g (0.02 mole) of 2-methyl-3-ethoxycarbonyl-4-hydroxythiophene and 0.15 mole of N,N-dimethylhydrazine acetate was heated with stirring at 90-110° for 10 min. The solution was cooled to room temperature, poured into 100 ml of ice water, and made alkaline to pH 9-9.5. The resulting dark oil was extracted with ether, and the ether solution was washed with water until it was neutral and then dried with magnesium sulfate. The ether was removed by distillation, and the residue was vacuum distilled to give 1.8 g (30.5%) of a product with bp 116° (2 mm) and n_D^{20} 1.5336. Found %: C 52.8; H 7.1; N 12.0; S 14.1. $C_{10}H_{16}N_2O_2S$. Calculated %: C 52.6; H 7.1; N 12.3; S 14.0.

3-Mercaptomethyl-4-ethoxycarbonyl-5-methylpyrazole (IV).* A mixture of 4.7 g (0.025 mole) of 2-methyl-3-ethoxycarbonyl-4-hydroxythiophene and 2.55 mole of hydrazine acetate was heated with stirring at 120-125° for 10 min. The solution was cooled to room temperature and poured into 250 ml of ice water. The pyrazole was extracted with ether, and the ether solution was dried with magnesium sulfate. The ether was removed by distillation, and the residue was recrystallized from ether to give 4.2 g (83%) of a product with mp 69-70°. Found %: C 48.2; H 5.9; N 14.2; S 16.3; mol. wt. 200 (from mass spectroscopy). $C_8H_{12}N_2O_2S$. Calculated %: C 48.0; H 6.0; N 14.0; S 16.0; mol. wt. 200.3.

3,5-Dimethyl-4-ethoxycarbonylpyrazole (V). A solution of 1.4 g (0.007 mole) of 3-mercaptomethyl-4-ethoxycarbonyl-5-methylpyrazole in 20 ml of dioxane was refluxed for 6 h with 10 g of Raney nickel. The catalyst was removed and washed with hot dioxane after cooling the mixture. The combined filtrates were evaporated to give 0.6 g (54%) of a product with mp 95-96° (from ether) (mp 96° [13]). This product did not depress the melting point of the 3,5-dimethyl-4-ethoxycarbonylpyrazole synthesized by the method in [13].

3-(2',4'-Dinitrophenyl)thiomethyl-4-ethoxycarbonyl-5-methylpyrazole (VI). A solution of 0.2 g (0.005 mole) of sodium hydroxide in 2 ml of water and a solution of 1 g (0.005 mole) of 2,4-dinitrochlorobenzene in 3 ml of methanol were added successively to a solution of 1 g (0.005 mole) of 3-mercaptomethyl-4-ethoxy-carbonyl-5-methylpyrazole in 4 ml of methanol. The mixture was heated on a water bath for 10 min and cooled. The crystals of VI were filtered and washed with water and methanol to give 1.4 g (76%) of a product with mp 177-178° (from methanol). Found %: C 46.1; H 4.0; N 15.1; S 8.8. $C_{14}H_{14}N_4O_6S$. Calculated %: C 45.9; H 3.8; N 15.3; S 8.7.

* 3-Mercaptomethyl-4-ethoxycarbonyl-5-methylpyrazole (IV) was also obtained by the action of hydrazine hydrate on a methanol solution of I at −5 to 0°.

The IR spectra of mineral oil suspensions of the substances obtained were recorded with a UR-10 spectrometer. The IR spectra of alcohol solutions were recorded with an EPS-3 spectrophotometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard.

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