ADDITION OF METHYL MERCAPTOACETATE TO N-VINYLPYRROLES

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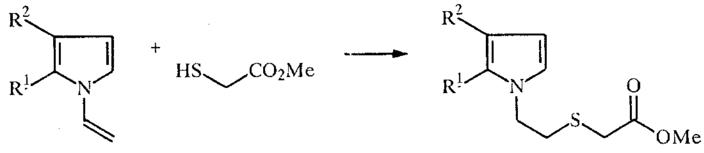
Methyl esters of 2-(pyrryl-1)ethylthioacetic acid were synthesized in 53-71% yield by addition of methyl mercaptoacetate to N-vinylpyrroles. Their reactions with ammonia and hydrazine hydrate were investigated.

Addition of mercaptoalkanecarboxylic acids and their derivatives as SH-addends to N-vinylpyrroles as a route to the formation of new groups of substituted pyrroles and a promising means of introducing pyrrole rings into complex molecules such as enzymes and biologically important amino acids that contain SH groups, in order to modify their properties.

The purpose of the present study was to develop a convenient method of synthesis of the novel functionally substituted pyrroles V-VIII by means of addition of the methyl ester of mercaptoacetic acid to N-vinylpyrroles I-IV.



I-IV

V-VIII

I, V R^1—R^2=$(CH_2)_4$; II, VI R^1=Me, R^2=*Pr;* III, VII *R^1*=Ph, R^2=H; IV, VIII R^1=Ph, R^2=Bu

The reaction readily proceeded at 70-80°C in the presence of azobisisobutyronitrile (AIBN, 1%) and was finished in 2.5-3 h. To synthesize VIII in acceptable yield (58%) it was necessary to increase the reaction time to 39 h. A shorter reaction time left starting material in the reaction mixture (GLC). In comparable conditions without the initiator, the yield of adducts V-VIII fell to 20%. The reaction is distinguished by its high selectivity. We were unable to detect even traces of side products in the reaction mixture at any stage. Chromatograms of the crude product and the product isolated by distillation were practically identical. The products are high-boiling yellowish liquids with unpleasant odors. Yields and physicochemical constants are given in Table 1. The PMR spectra of the adducts show no $RSCHCH_3$ proton signals and the character and integral intensities of the signals are completely in accord with pyrrole structures V-VIII, which points to the addition of the thiyl radical exclusively in the β position of the vinyl group (two methylene-group triplets, Table 2). In the IR spectra of V-VIII (thin film), the C=O valence vibrations give intense bands at 1720 cm^{-1}.

The reaction of pyrrole I with mercaptoacetic acid (ester, 20°C) yielded the dimer previously obtained from the same pyrrole in the presence of various acids [1-3] and orange—red polymeric products. The IR spectra showed the principal fragments to be conjugated double bonds, carbonyl groups, and NH and OH groups (strong, broad doublet in the 1620-1690 cm^{-1} region, broad, intense band in the 3100-3600 cm^{-1} region with a maximum at 3400 cm^{-1}). The cyclohexane rings were also in evidence (2850 and 2910 cm^{-1}). Vibrations of the pyrrole nucleus were absent.

The reaction of mercaptoacetic acid with pyrrole I under conditions of radical initiation (AIBN, 70-80°C, 5 h) used for the addition of thiols to N-vinylpyrroles [4] also failed to give the desired result. A glassy red polymer formed, the IR spectrum of which displayed a very intense band in the 2400-2750 cm^{-1} region with a maximum at 2400 cm^{-1} (acidic hydroxyl); the pyrrole ring frequencies were absent from the spectrum. Evidently the product of mercaptoacetic acid addition to pyrrole I polymerizes with opening of the pyrrole ring.

An attempt to use the sodium salt of mercaptoacetic acid as an addend (AIBN, EtOH, 70°C) to N-vinylpyrroles was also unsuccessful; pyrrole I was completely transformed in the reaction.

As is well known, amide groups are important components of many biologically active compounds. Amides with heterocyclic groups display pharmacological activity [5-8], leading to increased interest in the chemistry of these compounds.

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TABLE 1. Physicochemical Characteristics of Pyrroles V-X

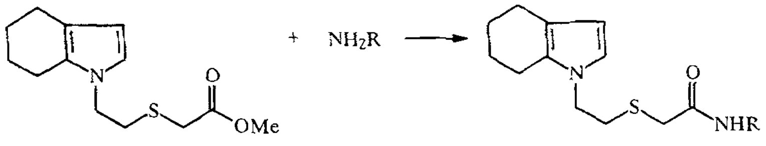
Compound	Elemental formula	Bp, °C (GPa) [mp, °C]	n_D^{20}	d_4^{20}	Yield, %
V	$C_{13}H_{19}NO_2S$	177 (1,33)	1,5440	1,4447	67
VI	$C_{13}H_{21}NO_2S$	165...171 (1,33)	1,5155	1,0699	71
VII	$C_{15}H_{17}NO_2S$	185 (1,33)	1,5786	1,1688	53
VIII	$C_{19}H_{25}NO_2S$	215...225 (1,33)	1,5587	1,1077	58
IX	$C_{12}H_{18}N_2OS$	[72...73]			82
X	$C_{12}H_{19}N_3OS$	[58...59]			79

TABLE 2. PMR Spectra of Pyrroles V-VIII

Compound	Chemical shifts, δ, ppm							
	NCH_2CH_2	SCH_2CH_2	SCH_2CO_2	Me	2-H	3-H	R^1	R^2
V	3,98	2,87	3,09	3,66	6,53	5,75	1,72	2,42; 2,54
VI	3,98	2,87	2,97	3,70	6,57	5,92	2,13	0,90; 1,50; 2,33
VII	4,16	2,77	2,90	3,65	6,79	6,20	7,36	6,20
VIII	3,95	2,61	2,79	3,58	6,65	6,06	7,29	0,78; 1,35; 2,33

Esters V-VIII readily form amides and hydrazides, as demonstrated using pyrrole V as a model.

Amide IX was prepared in 82% yield by brief heating of pyrrole V with aqueous ammonia. The PMR spectrum of IX lacks the methoxy group protons at 3.66 ppm and displays a NH_2 group signal at 6.98 ppm. The IR spectrum of IX shows the NH_2 valence vibration band (doublet at 3360 cm^{-1}, antisymmetric vibration; 3160 cm^{-1}, symmetrical vibration) and an intense band at 1649 cm^{-1} (C=O).



V

IX, X

IX R=H; X R=NH_2

Hydrazide X was prepared by heating pyrrole V with hydrazine hydrate. In the IR spectrum the bands corresponding to the C=O valence vibrations have complex structure (1655, 1615 cm^{-1}) associated with the participation of the C=O group in an intermolecular hydrogen bond, while a broad band in the 3100-3400 cm^{-1} region with a poorly resolved maximum is also witness to the strong association. In CCl_4 solutions the C=O band is displaced toward higher frequency (1678 cm^{-1}) and the NH valence vibrations have frequencies of 3350, 3400, and 3440 cm^{-1}, close to the ν_{NH} values for hydrazides [9].

EXPERIMENTAL

IR spectra of pyrroles V-X were recorded on a Specord IR-75 spectrophotometer as thin films (V-VIII) or in KBr discs (IX, X). PMR spectra were recorded on a Bruker WP-200 SY (200, 13 MHz) in acetone-d_6 with a TMS standard. The reaction progress and the purity of the products were monitored with a Khrom-5 (Czechoslovakia) gas chromatograph (catharometric detector, helium carrier gas, column 3 × 1000 mm, liquid phase 5% silicon DC-550, column temperature 220°C, detector 220°C, injector 300°C) and by TLC on Silufol UV-254 plates with hexane—ether (1:1, 19:1 elution).

The results of elemental analysis of the newly synthesized compounds agreed with the calculated values.

Methylmercaptoacetate. A mixture of 62.6 g (0.68 mole) mercaptoacetic acid, 72.3 g (2.48 mole) absolute methanol, and 14 g (0.14 mole) H_2SO_4 was let stand 2 days at room temperature. The reaction mixture was poured into ice water and extracted with ether, and vacuum redistillation yielded 35 g methyl mercaptoacetate, bp 45-47°C (18.6 GPa).

Methyl Ester of 2-(4,5,6,7-tetrahydroindolyl-1)ethylthioacetic Acid. A. Pyrrole I (1.47 g, 0.01 mole) was heated at 70-80°C for 2 h with 1.06 g (0.01 mole) methyl mercaptoacetate. Vacuum redistillation yielded 0.5 g (20%) of ester V.

B. Pyrrole I (1.47 g, 0.01 mole) was heated at 70-80°C for 2 h with 1.06 g (0.01 mole) methyl mercaptoacetate and 0.01 g AIBN. Vacuum distillation yielded 1.69 (67%) of ester V.

Esters VI and VII were prepared analogously with the method of **B.**

Methyl Ester of 2-(2-Phenyl-3-n-butylpyrryl-1)ethylthioacetic Acid (VIII). Pyrrole IV (13.6 g, 0.06 mole) was heated at 70-80°C for 39 h with 6.36 g (0.06 mole) of methyl mercaptoacetate and 0.05 g AIBN. Vacuum redistillation yielded 11.6 g (58%) of ester VIII.

Reaction of 1-Vinyl-4,5,6,7-tetrahydroindole (I) with Mercaptoacetic Acid. A. To a solution of 1.47 g (0.01 mole) of pyrrole I in 40 ml diethyl ether was added over 1 h at room temperature a solution of 0.92 g (0.01 mole) of mercaptoacetic acid in 10 ml diethyl ether. The reaction mixture was stirred for 6 h and left overnight, then washed with 1 M KOH (10 ml). The residue after removal of the ether was dissolved in hexane with warming, a part of the material (0.6 g) remaining undissolved. Cooling gave a crystalline precipitate (0.5 g) representing (TLC, hexane—ether, 19:1) a mixture of the dimer of 1-vinyl-4,5,6,7-tetrahydroindole [1-3] and soluble polymers.

B. Pyrrole I (1.47 g, 0.01 mole) was heated at 70-80°C for 5 h with mercaptoacetic acid and 0.01 g AIBN. A glassy red substance formed, which was dissolved in benzene and precipitated from hexane. A polymer (2 g) was separated as powder. IR: 1700 (C=O), 2400-2750, maximum 2500 cm^{-1} (acidic hydroxyl).

Reaction of 1-Vinyl-4,5,6,7-tetrahydroindole with the Sodium Salt of Mercaptoacetic Acid. NaOH (0.4 g, 0.01 mole) was dissolved in 50 ml EtOH and 0.92 g (0.01 mole) mercaptoacetic acid were added. The resulting salt was insoluble in EtOH. To this heterogeneous system was added, over 1 h, 1.47 g (0.01 mole) of pyrrole I, the mixture was stirred for 5 h, and the salt crystals were filtered out. After removal of the EtOH 1.32 g of pyrrole I were separated, the mp and IR spectrum of which were those of the known sample.

Amide-2-(4,5,6,7-tetrahydroindolyl-1)ethylthioacetic Acid (IX). Pyrrole V (1 g, 0.004 mole) was stirred in 20 ml of 25% aqueous ammonia at 45-50°C for 2 h and the crystals were filtered off and recrystallized from hexane. Yield 0.77 g (82%) of amide IX, mp 72-73°C. PMR (DMSO-d_6): 6.98 (2H, s, NH_2); 6.53 (1H, d, 2-H); 5.70 (1H, d, 3-H); 3.90 (2H, t, NCH_2CH_2); 3.03 (2H, s, SCH_2CO); 2.71 (2H, t, SCH_2CH_2); 2.25, 1.67 ppm [8H, m, $-(CH_2)_4-$].

Hydrazide of 2-(4,5,6,7-Tetrahydroindolyl-1)ethylthioacetic Acid (X). Pyrrole V (0.25 g, 0.001 mole) was stirred with 0.3 g (0.001 mole) of 20% hydrazine hydrate at 80°C for 1.5 h. An oily substance was separated which crystallized on standing in the refrigerator for 2 days; mp 58°C after recrystallization from hexane. PMR (DMSO-d_6): 6.54 (1H, d, 2-H); 5.70 (1H, d, 3-H); 3.90 (2H, t, NCH_2CH_2); 3.01 (2H, s, SCH_2CO); 2.80 (2H, t, SCH_2CH_2); 2.38, 1.67 ppm [8H, m, $-(CH_2)_4-$].

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