FUNCTIONAL DERIVATIVES OF THIOPHENE

VII.* o-HALONITROTHIOPHENES IN THE SYNTHESIS OF THIENOPYRROLES

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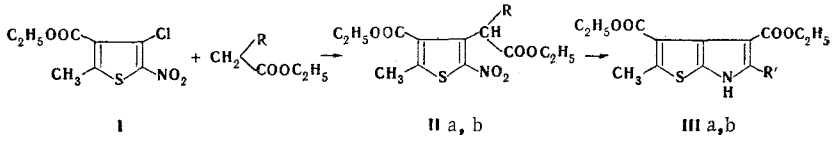
The derivatives obtained by reaction of o-halonitrothiophenes with cyanoacetic and acetoacetic esters were converted to thieno[2,3-b]- and thieno[3,2-b]pyrroles by reductive cyclization.

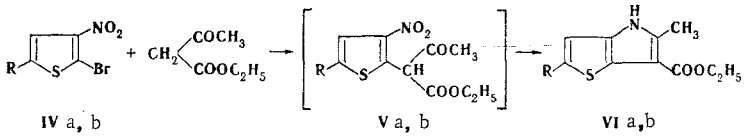
The interest in thienopyrroles as isosteres of indole has been responsible for the development of research on thieno[2,3-b]- and thieno[3,2-b]pyrrole derivatives [2]. We have found that thienopyrroles can be synthesized from o-halonitrothiophenes by the method known for the preparation of indole derivatives [3, 4]. The reaction of 2-methyl-3-carbethoxy-4-chloro-5-nitrothiophene [5] (I) with the sodium derivative of cyanoacetic ester gives 2-methyl-3-carbethoxy-5-nitro-4-thienylcyanoacetic ester (IIa), which is converted to thieno[2,3-b]pyrrole (IIIa) under the conditions of reductive cyclization. We were unable to isolate pure acetoacetic ester derivative IIb, obtained in a manner similar to that used to prepare IIa. Without additional purification, IIb was converted to thieno[2,3-b]pyrrole (IIIb) under the conditions of reductive cyclization.



I — II a, b — III a,b

II a R=CN; b R=$COCH_3$; III a R′=NH_2; b R′=CH_3

We obtained the thieno[3,2-b]pyrroles (VIa, b) from 2-bromo-3-nitrothiophenes (IVa, b) [6, 7] and the sodium derivative of acetoacetic ester.



IV a, b — V a, b — VI a,b

IV-VI a R=$COCH_3$; b R=$COOC_2H_5$

We were able to carry out the reductive cyclization of intermediates IIa, b and Va, b by the action of anhydrous tin chloride in ether saturated with hydrogen chloride or by the action of iron in the presence of ferrous sulfate in aqueous dioxane.

As in the spectrum of N-benzylthieno[2,3-b]pyrrole [8], one absorption maximum is observed in the UV spectrum of thieno[2,3-b]pyrrole IIIb. Donor–acceptor substituents in IIIb lead to a bathochromic shift of this band and to an increase in its intensity. The appearance of a second maximum in the spectrum of

* See [1] for communication VI.

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IIIa is probably caused by the presence in it of carbethoxy and amino groups conjugated with the pyrrole ring and interacting with one another; this is in good agreement with the literature data [8]. As in the spectrum of N-benzylthieno[3,2-b]pyrrole [8], the spectra of thieno[3,2-b]pyrroles contain two absorption maxima – the first at ~250 nm and the second of high intensity at 320 nm.

A singlet of 3-H protons at 7.6 and 7.7 ppm can be noted in the PMR spectra of thieno[3,2-b]pyrroles VIa, b. The chemical shift of this proton in substituted thieno[3,2-b]pyrrole is 6.6 ppm [8]. The observed deshielding effect of the carbonyl-containing substituents of VIa, b on the chemical shift of the 3-H protons is comparable to the corresponding values for other thieno[3,2-b]pyrrole derivatives [9].

EXPERIMENTAL

The UV spectra of alcohol solutions were recorded with a Hitachi EPS-3 recording spectrophotometer. The PMR spectra of deuterochloroform solutions were recorded with a JEOL JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard.

2-Methyl-3-carbethoxy-5-nitro-4-thienylacetic Ester (IIa). A suspension of 0.9 g (0.04 mole) of sodium in 80 ml of absolute benzene was treated with 5 ml (0.04 mole) of cyanoacetic ester, and the mixture was heated until all of the sodium had undergone reaction. A solution of 5 g (0.02 mole) of I in 20 ml of absolute benzene was added by drops with stirring to the resulting suspension of the sodium derivative in benzene, and the mixture was stirred and refluxed for 6 h. It was then cooled and treated with 2% sodium carbonate solution. The sodium carbonate extract was acidified carefully with dilute hydrochloric acid (1 : 1) until it was acidic to Congo Red. The resulting oil began to crystallize, after which it was removed by filtration and washed with isopropyl alcohol to give 3.5 g (55.3%) of IIa with mp 90-91° (from isopropyl alcohol). Found: C 48.0; H 4.4; N 8.5; S 9.9%. $C_{13}H_{14}N_2O_6S$. Calculated: C 47.8; H 4.3; N 8.6; S 9.9%.

2-Methyl-3,4-dicarbethoxy-5-aminothieno[2,3-b]pyrrole (IIIa). A suspension of 5.8 g (0.03 mole) of tin chloride in 45 ml of absolute ether was saturated, with stirring and ice cooling, with dry hydrogen chloride. When two layers had formed in the reaction mixture, a solution of 2 g (0.06 mole) of IIa in 140 ml of absolute ether was added to it, and the mixture was stirred at 25-30° for 4 h. The ether layer was decanted from the resulting precipitate, and the precipitate was suspended in 50 ml of water. The suspension was made alkaline to pH 9 with 10% sodium hydroxide solution, and the solid was removed by filtration to give 1.2 g (66%) of IIIa with mp 144-145° (from methanol). UV spectrum, λ_{max}, nm (log ε): 266 (4.06), 300 (3.90); λ_{min}, nm (log ε): 250 (3.98), 284 (3.87). Found: C 52.9; H 5.6; N 9.5; S 10.7%. $C_{13}H_{16}N_2O_4S$. Calculated: C 52.7; H 5.4; N 9.5; S 10.8%.

2,5-Dimethyl-3,4-dicarbethoxythieno[2,3-b]pyrrole (IIIb). The method used to prepare IIa was used to obtain IIb from 0.9 g (0.04 mole) of sodium in 80 ml of absolute benzene, 5.6 ml (0.04 mole) of acetoacetic ester, and 5 g (0.02 mole) of I in 20 ml of absolute benzene. After acidification of the sodium carbonate extract, the resulting oil (IIb) was dissolved in 35 ml of 65% aqueous dioxane. A 3.4-g (0.06 g-atom) sample of iron filings* and 0.4 g of ferrous sulfate were added to the resulting solution, and the mixture was heated and stirred thoroughly at 100° for 1.5 h. The sediment was removed by filtration and washed with hot dioxane. The combined dioxane solutions were diluted with water, and the resulting precipitate was removed by filtration and dried to give 2.5 g (45%) of IIIb with mp 128-129° (from methanol). UV spectrum, λ_{max}, nm (log ε): 266 (4.15); λ_{min}, nm (log ε): 238 (3.78). Found: C 56.9; H 5.7; N 4.8; S 11.0%. $C_{14}H_{17}NO_4S$. Calculated: C 56.9; H 5.8; N 4.7; S 10.8%.

2-Acetyl-5-methyl-6-carbethoxythieno[3,2-b]pyrrole (VIa). A solution of 5.6 ml (0.04 mole) of acetoacetic ester and 4.1 g (0.02 mole) of IVa in 80 ml of absolute tert-butyl alcohol was added to a solution of 0.9 g (0.04 mole) of sodium in 40 ml of absolute tert-butyl alcohol, and the mixture was refluxed for 3.5 h, cooled, and acidified with dilute hydrochloric acid (1 : 1) until it was acid to Congo Red. The alcohol was then removed by vacuum distillation at 30-40°. The residue was extracted with ether, and the ether layer was washed with water until it was neutral; it was then extracted with 2% aqueous sodium carbonate. The sodium carbonate extracts were acidified with dilute hydrochloric acid and extracted with ether. The ether extract was dried with magnesium sulfate, and the solvent was removed by distillation. A 70-ml sample of 65% aqueous dioxane, 3.4 g (0.06 g-atom) of iron filings, and 0.4 g of ferrous sulfate were added to the residue, and reductive cyclization was carried out under the conditions of the preceding experiment. The resulting precipitate was dried, dissolved in 10 ml of ethyl acetate, and chromatographed on a column

*Iron filings with a particle size of less than 0.25 mm were used for the experiment.

filled with activity-II aluminum oxide (elution with ethyl acetate) to give 1.4 g (28%) of VIa with mp 197.5-198.5° (from methanol). UV spectrum, λ_{max}, nm (log ε): 250 (3.74), 346 (4.00); λ_{min}, nm (log ε): 220 (3.30), 292 (3.28). Found: C 57.4; H 5.3; N 5.8; S 12.7%. $C_{12}H_{13}NO_3S$. Calculated: C 57.3; H 5.2; N 5.6; S 12.8%.

2,6-Dicarbethoxy-5-methylthieno[3,2-b]pyrrole (VIb). The method used to prepare Va was used to obtain Vb from 0.9 g (0.04 mole) of sodium in 40 ml of absolute tert-butyl alcohol, 5 ml (0.04 mole) of acetoacetic ester, and 5 g (0.02 mole) of IVb in 60 ml of absolute tert-butyl alcohol. As in the preparation of IIIb, VIb was obtained by adding to Vb 3.4 g (0.06 g-atom) of iron filings and 0.4 g of ferrous sulfate in 70 ml of 65% aqueous dioxane. The yield of VIb, with mp 167.5-168.5° (from methanol), was 0.7 g (14%). UV spectrum, λ_{max}, nm (log ε): 250 (4.05), 323 (4.35); λ_{min}, nm (log ε): 220 (3.60), 285 (3.91). Found: C 55.5; H 5.5; N 4.9; S 11.5%. $C_{13}H_{15}NO_4S$. Calculated: C 55.5; H 5.4; N 5.0; S 11.4%.

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