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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 70th Anniversary

Synthesis and Complexing Properties of Alkyl (3-Oxo-2,3-dihydrothiophen-2-ylidene)- and (4-Oxothiazolidin-5-ylidene)acetate Derivatives

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Abstract—Condensation of dimethyl and diethyl acetylenedicarboxylate with thioacetamides gave the corresponding alkyl (3-oxo-2,3-dihydrothiophen-2-ylidene)- and (4-oxothiazolidin-5-ylidene)acetates. Treatment of these compounds with zinc in acetic acid resulted in reduction of the exocyclic double bonds. The products can be used in membrane processes as sodium cation carriers.

Extensive studies in the field of membrane transfer processes, which play an important role in biological systems, have started at the end of the 20th century [1]. The synthesis of first receptor molecules capable of selectively binding organic and inorganic substrates gave an impetus to development of a new interdisciplinary field of chemistry, namely supramolecular chemistry [2]. Apart from recognition and catalysis, transport is an integral feature of supramolecules and is a fundamental process in supramolecular chemistry.

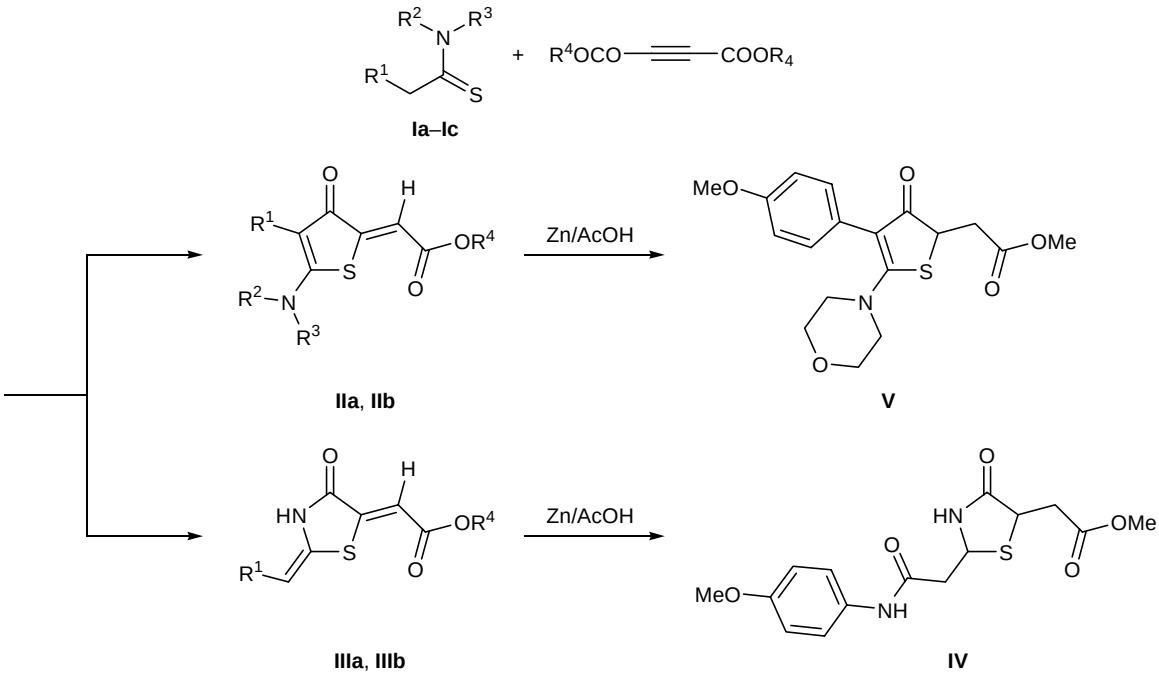
Selective membrane permeability is ensured by carrier molecules which are present in a liquid membrane and are capable of selectively reacting with a compound to be transferred [3]. Carrier molecules determine the nature of substrates transferred through a membrane and such physical parameters of mass transfer as rate, selectivity, and type of the process. Variation of the receptor structure makes it possible to control the transfer process and analyze effects of structural factors on the thermodynamic and kinetic parameters [4].

Heterocycles possessing exocyclic trisubstituted double bonds attract attention due to their specific geometry. The presence of a carbonyl group in the *ortho* position with respect to the endocyclic heteroatom implies that such compounds can be used as ligands for complex formation with various metal ions. We previously developed a new convenient procedure for the synthesis of 2,5-dimethylenethiazolidin-4-ones and 2-methylenethiophenes via reaction of thioacetamides with dimethyl acetylenedicarboxylate (DMAD) [5, 6]. The goal of the present work was to obtain new thiophene and thiazole derivatives containing an ethoxycarbonylmethylene group in the 2-position and examine the possibility of using such heterocyclic compounds as ligands for membrane transfer of sodium salts.

We have found that, depending on the initial thioacetamide, the reaction with acetylenedicarboxylic acid esters leads to formation of thiophenes **IIa** and **IIb** or 2,5-dimethylenethiazolidin-4-ones **IIIa** and **IIIb**. The latter were obtained from thioamide **Ic** which has no substituents at the nitrogen atom (Scheme 1).

Treatment of compound **IIIa** with metallic zinc in acetic acid at room temperature afforded a mixture of products, and the conversion of **IIIa** was not complete. When the reaction was carried out at 60–70°C, a single product was formed. Its ^{1}H NMR spectrum contained

Scheme 1.



I, **II**, R^1 = 4-$MeOC_6H_4$, R^2R^3N = morpholino, R^4 = Me (**a**); R^1 = 4-BrC_6H_4, R^2R^3N = morpholino, R^4 = Et (**b**); **Ic**, R^1 = 4-$MeOC_6H_4NHCO$, R^2 = R^3 = H; **III**, R^1 = 4-$MeOC_6H_4NHCO$, R^4 = Me (**a**), Et (**b**).

signals from two NH protons at δ 9.76 and 8.58 ppm, two two-proton doublets from aromatic protons at δ 7.43 and 6.78 ppm, two three-proton singlets from two methoxy groups at δ 3.89 and 3.66 ppm, and six one-proton doublets of doublets at δ 4.93 (J = 8.5, 4.6 Hz), 3.97 (J = 4.2, 9.6 Hz), 3.01 (J = 16.8, 4.2 Hz), 2.94 (J = 14.9, 4.6 Hz), 2.70 (J = 16.8, 9.6 Hz), and 2.62 ppm (J = 14.9, 8.5 Hz). The latter were assigned to two $CHCH_2$ groups. Taking into account these data and also the presence of the molecular ion peak with m/z 338 (47%) in the mass spectrum, the product was assigned the structure of thiazolidine **IV**.

Our attempts to reduce the exocyclic double bond in thiophene derivatives **IIa** and **IIb** under analogous conditions resulted in decomposition of the thiophene ring. The reaction with thiophene **IIa** at reduced temperature was complete in less than 30 min, and we isolated 20% of 2,3-dihydrothiophene **V**. In the ^{1}H NMR spectrum of the product we observed signals from aromatic protons as two two-proton doublets at δ 7.06 and 6.90 ppm (J = 8.5 Hz), two methoxy groups as two three-proton singlets at δ 3.75 and 3.64 ppm, protons of the morpholine fragment as a multiplet at δ 3.20–3.35 ppm, and three one-proton doublets of doublets at δ 4.05 (J = 10.7, 3.7 Hz), 3.15 (J = 17.1, 3.7 Hz), and 2.62 ppm (J = 17.1, 10.7 Hz) which were assigned to 2-H and 2-CH_2.

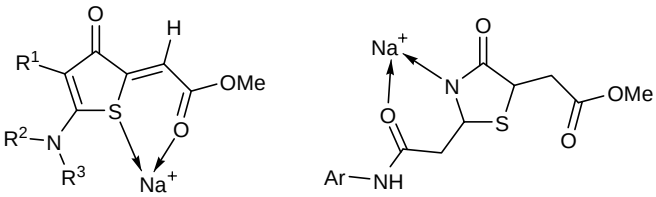
Using the NMR titration technique, we previously [7] found that thiazolidinones structurally related to **III** are capable of forming complexes with sodium cation. In the present work we examined complexing properties of compounds **IIa**, **IIb**, and **IV** by the membrane transfer technique. The ion fluxes of sodium salts through an impregnated liquid membrane are given in table together with the results of blank experiment in which the membrane contained no carrier. It is seen that thiophene derivatives **IIa** and **IIb** insignificantly increase the rate of ion transport and that the latter weakly depends on the anion nature.

Initial ion fluxes through impregnated liquid membranes (temperature 20°C)

Compound no.	Ion flux, (mol s^{-1} m^{-2}) × 10^{-6}		
	$Na_2Cr_2O_7$	Na_2SO_4	NaCl
IVa	9.60	6.72	15.5
IIa	0.146	0.172	0.437
IIb	0.146	0.162	0.475
Blank experiment	0.0750	0.0735	0.0644

Thiazolidine derivative **IV** ensures a higher transfer rate. These data may be interpreted in terms of formation of dative bonds involving the ester carbonyl oxygen atom and sulfur atom in thiophenes **II** or carbamoyl oxygen atom and ring nitrogen atom in **IV**, as shown in Scheme 2 [7].

Scheme 2.



Thus we have developed a procedure for the synthesis of hydrogenated sulfur-containing heterocycles having methylene and alkoxycarbonylmethylene substituents and demonstrated the possibility of using the products as carriers for transfer of sodium cations through an impregnated liquid membrane.

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using the following solvent systems: chloroform, chloroform–ethanol (9:1, 15:1, 20:1), and ethyl acetate–hexane (1.5:2, 1:2). The NMR spectra were recorded on Bruker WM-250 (250 MHz for ^{1}H) and Bruker DRX-400 spectrometers (400 MHz for ^{1}H and 100 MHz for ^{13}C) using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on Varian MAT 311A and Finnigan MAT 8200 instruments with direct sample admission into the ion source. The solvents were dried and purified by standard procedures.

Methyl 2-[(*Z*)-4-(4-methoxyphenyl)-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate (IIa). Dimethyl acetylenedicarboxylate, 0.1 mol, was added to a solution of 0.1 mol of 1-morpholino-2-(4-methoxyphenyl)ethanethione (**Ia**) in 10 ml of anhydrous ethanol, and the mixture was heated for 2 h under reflux. The solvent was distilled off, the residue was ground with alcohol, and the precipitate was filtered off and recrystallized from chloroform–hexane. Yield 50%, mp 159–161°C; published data [6]: mp 160°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.44–3.48 m (4H, $2CH_2$), 3.60–3.64 m (4H, $2CH_2$), 3.76 s (3H, OCH_3), 3.77 s (3H, OCH_3), 6.63 s (1H, CH), 6.93 d (2H, H_{arom}, J = 6.8 Hz), 7.16 d (2H, H_{arom}, J = 6.8 Hz). Found, %: N 4.12; S 8.97. $C_{18}H_{19}NO_5S$. Calculated, %: N 3.88; S 8.86.

Ethyl 2-[(*Z*)-4-(4-bromophenyl)-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate (IIb) was synthesized in a similar way using diethyl acetylenedicarboxylate. Yield 65%, mp 184°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (3H, CH_3, J = 7.1 Hz), 3.44–3.46 m (4H, $2CH_2$), 3.60–3.64 m (4H, $2CH_2$), 4.25 q (2H, OCH_2, J = 7.1 Hz), 6.61 s (1H, CH), 7.25 d (2H, H_{arom}, J = 6.8 Hz), 7.60 d (2H, H_{arom}, J = 7.0 Hz). Mass spectrum, m/z (I_{rel}, %): 425 (29), 423 (30). Found, %: N 3.64; S 8.01. $C_{18}H_{18}BrNO_4S$. Calculated, %: N 3.30; S 7.56.

Methyl 2-[(2*E*,5*Z*)-2-(4-methoxyphenylcarbamoylmethylene)-4-oxothiazolidin-5-ylidene]acetate (IIIa). Dimethyl acetylenedicarboxylate, 0.4 ml (3.17 mmol), was added at room temperature to a suspension of 3 mmol of thioacetamide **Ic** in 30 ml of ethanol (or 40 ml of chloroform, or 2 ml of DMSO). The mixture was stirred for 2 h and cooled, and the precipitate was filtered off and recrystallized from alcohol. Yield 85%, mp 128–129°C; published data [7]: mp 128°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.72 s (3H, OMe), 3.77 s (3H, OMe), 5.85 s (1H, $CH=C^2$), 6.69 s (1H, $CH=C^5$), 6.87 d (2H, H_{arom}, J = 9.2 Hz), 7.52 d (2H, H_{arom}, J = 9.2 Hz), 9.85 s (1H, NH), 12.33 br.s (1H, NH). Found, %: N 8.38; S 9.95. $C_{15}H_{14}N_2O_5S$. Calculated, %: N 8.38; S 9.59.

Ethyl 2-[(2*E*,5*Z*)-2-(2-methoxyphenylcarbamoylmethylene)-4-oxothiazolidin-5-ylidene]acetate (IIIb) was synthesized as described above for compound **IIIa** using diethyl acetylenedicarboxylate. Yield 80%, mp 128–129°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.12 t (3H, Me, J = 7.0 Hz), 4.12 q (2H, OCH_2, J = 7.0 Hz), 5.82 s (1H, $CH=C^2$), 6.68 s (1H, $CH=C^5$), 7.0–7.2 m (4H, H_{arom}), 9.85 s (1H, NH), 12.33 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 398 (47), 396 (46). Found, %: N 7.22; S 7.95. $C_{15}H_{13}BrN_2O_4S$. Calculated, %: N 7.05; S 8.07.

Methyl 2-[2-(4-methoxyphenylcarbamoylmethyl)-4-oxothiazolidin-5-yl]acetate (IV). Metallic zinc, 6 mmol, was added at room temperature to a suspension of 3 mmol of thiazolidinone **IIIa** in 10 ml of glacial acetic acid. The mixture was heated for 2 h under reflux, an additional 6 mmol of zinc was added, and the mixture was heated for 6 h under reflux, cooled, and filtered from the undissolved material. The filtrate was extracted with chloroform (3×100 ml), the extract was washed with water and evaporated, and

the residue was recrystallized from chloroform–hexane. Yield 75%, mp 190°C. ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 38.97 (CH_2), 42.11 (C^5), 45.16 (CH_2), 51.69 (C^2), 51.77 (OCH_3), 55.14 (OCH_3), 113.82 (CH_{arom}), 120.71 (CH_{arom}), 131.95 (NC_{arom}), 155.22 (OC_{arom}), 166.97 (CONH), 171.12 (**C**OOMe), 173.47 (C^4). Mass spectrum, *m*/*z* (I_{rel}, %): 338 (47). Found, %: N 7.92; S 9.35. $C_{15}H_{18}N_2O_5S$. Calculated, %: N 8.28; S 9.48.

Methyl 2-[4-(4-methoxyphenyl)-5-morpholino-3-oxo-2,3-dihydro-2-thienyl]acetate (V). Metallic zinc, 6 mmol, was added to a suspension of 3 mmol of thiophene **IIa** in 10 ml of glacial acetic acid at 15–18°C. The mixture was stirred for 30 min, 50 ml of water was added, and the product was extracted into methylene chloride (3×30 ml). The extract was dried and evaporated, and the residue was purified by flash chromatography using CH_2Cl_2 as eluent. Yield 20%, oily substance. Mass spectrum, *m*/*z* (I_{rel}, %): 363 (17). Found, %: N 3.92; S 8.53. $C_{18}H_{21}NO_5S$. Calculated, %: N 3.85; S 8.82.

Ion transport through a liquid membrane. The electric conductivity of solutions was measured with a Radelkis OK-102 conductometer. The ion fluxes through impregnated liquid membranes were measured in a glass beaker using a platinum electrode. Liquid membranes were prepared by impregnation of a poly(tetrafluoroethylene) membrane (Sigma–Aldrich; diameter 25 mm, pore diameter 0.2 μm) with a solution of 0.02 mmol of carrier in 0.02 ml of *o*-nitrophenyl octyl ether. The exhaustible phase was a 1 M solution of the corresponding salt. The substrate concentration in the receiving phase (distilled water, V = 400 ml) was determined by measuring the conductivity.

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