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Synthesis of Substituted Alkoxythiophenes: Thiophene Analogues of Dazoxiben

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Summary. The synthesis of the thiophene analogue of dazoxiben – one of the most selective TXA_2-synthase inhibitors – and its derivatization to a chlorinated, more lipophilic product is described. The ethylenoxy moiety was introduced *via* nucleophilic aromatic substitution of halogenated thiophene carboxylic esters, the imidazol residue, by use of a *t*-butoxy group as a synthon after ether cleavage and halogenation. Also, at this step chlorination of the thiophene moiety was carried out. After ester hydrolysis the target compounds were obtained as hydrochlorides.

Keywords. Thromboxane; Alkoxythiophene; Alkylimidazol.

Synthese von substituierten Alkoxythiophenen: Thiophenanaloga von Dazoxiben

Zusammenfassung. Die Synthese des Thiophenanalogons von Dazoxiben – eines hoch selektiven TXA_2-Synthase-Inhibitors – und seine Derivatisierung zu einem chlorierten, stärker lipophilen Produkt wird beschrieben. Die Ethylenoxy-Gruppierung wurde durch nucleophile aromatische Substitution von halogenierten Thiophencarbonsäureestern eingeführt, Imidazol unter Verwendung einer *t*-Butoxygruppe als Synthon (nach Etherspaltung und Halogenierung). Auf dieser Stufe erfolgte außerdem die Chlorierung am Thiophenteil. Nach Esterhydrolyse wurden die Zielverbindungen als Hydrochloride erhalten.

Introduction

When a cell membrane is damaged, arachidonic acid is liberated which is then converted into prostaglandines, prostacyclines, and thromboxanes by a metabolic pathway involving the enzyme cyclooxygenase. One of them – thromboxane A_2 (TXA_2) [1] – is an extremely potent vasoconstricting and platelet aggregating agent and plays an important role in a number of pathophysiological situations like pulmonary hypertension, circulatory shock, or ischemia. On the other hand, prostaglandines and prostacyclines (*PGI*) show beneficial effects during these disorders; *i.e.*, *PGI* is a potent vasodilator and antiaggregatory agent.

Although there has been continuous search for selective TXA_2-synthase inhibitors, many of them exhibit non-specific activities such as stimulation of platelet phosphodiesterase or inhibition of cyclooxygenase, or they are endoper-

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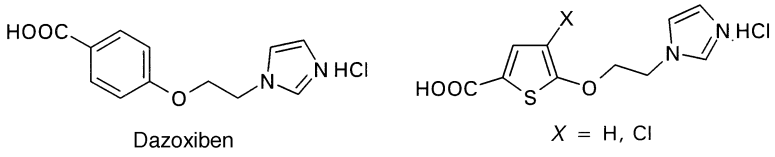
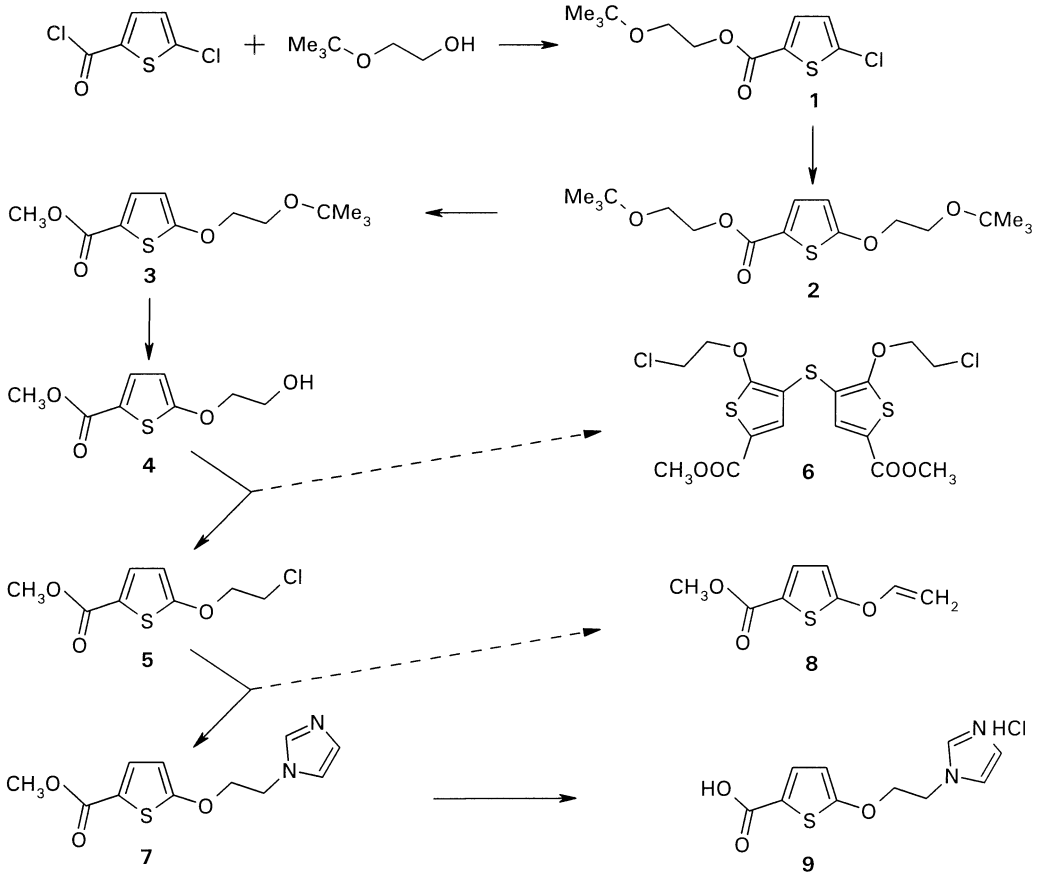


Fig. 1. Dazoxiben and its new thiophene analogues

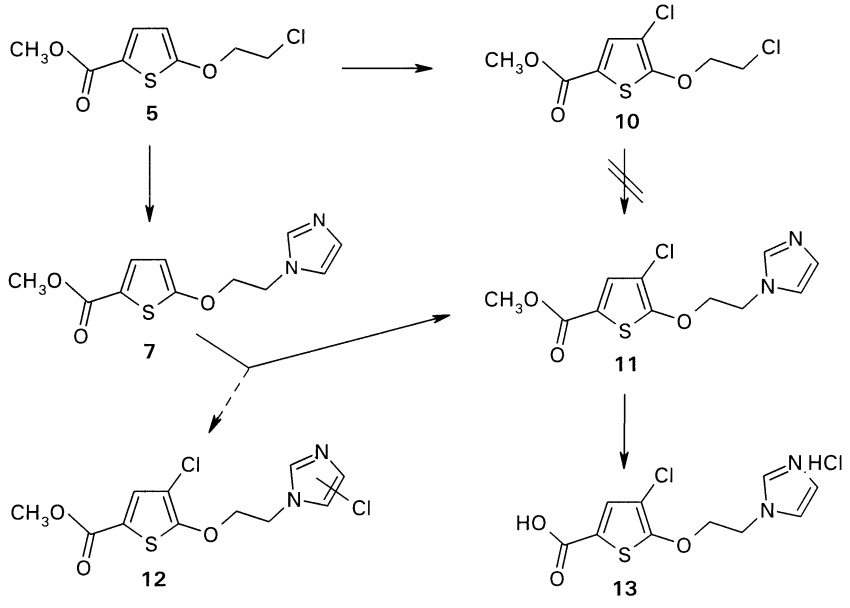
oxide/thromboxane antagonists or agonists. Since the bioisosteric exchange of benzene by thiophene has often led to an improved physiological effect, we decided to apply this concept on dazoxiben [2], one of the most selective TXA_2-synthase-inhibitors.

Results and Discussion

The synthesis of dazoxiben is based on the O-alkylation of the *p*-hydroxybenzoic acid ester sodium salt with 1,2-dibromoethane and subsequent substitution with imidazol [2]. As the high *ene*-character of 2-hydroxythiophenes complicates a selective analogous reaction [3], we introduced the ethylenoxy moiety *via* nucleophilic aromatic substitution (Scheme 1). With respect to transesterification, tested with various combinations of 5-halo-thiophene carboxylic esters and alcohols, the same residue was chosen for the ester group and the reagent, carrying the *t*-butoxygroup as a synthon for imidazol. Starting material **1** was obtained by reaction of 5-chloro-2-thiophene carboxylic acid chloride [4] with *t*-butoxy-ethanol [5] in the presence of triethylamine in 80% yield. After treatment with sodium *t*-butoxy ethanolate in N,N-dimethylformamide, the crude substitution product **2** was transformed into its methyl ester **3** by sodium methanolate in boiling methanol, giving an overall yield of 60%. Subsequently, the protective group could be cleaved selectively by short heating in concentrated hydrochloric acid. Although chlorination of **4** could now easily be achieved by thionyl chloride and pyridine as base, careful temperature control was important: reagent addition between -40 and -25°C and subsequent heating at 60°C for one hour yielded 91% of the desired product **5**. Without cooling, the temperature raised to 60°C, leading to 22% of thioether **6**, elemental sulfur, and only 25% of the chloro derivative **5**. This may be explained by an electrophilic substitution of thiophene in position 4 by thionyl chloride, reduction of the sulfinic acid derivative by disproportionation or other sulfur compounds, and subsequent electrophilic reaction of the reactive intermediate, *e.g.*, a sulfenyl chloride, with a second mol of **4**. The imidazol moiety was now introduced by substitution with sodium imidazolate in N,N-dimethylformamide at 70°C in the presence of catalytic amounts of sodium iodide in 53% yield. Independent of the order of reagent addition, *i.e.* even when sodium imidazolate was added slowly to chloride **5**, up to 28% of vinylether **8** was isolated due to elimination of hydrogen chloride under basic conditions. Ester **7** was now hydrolyzed with aqueous sodium hydroxide at room temperature, and hydrochloride **9** was directly obtained after acidification with hydrochloric acid by precipitation from ethanol with tetrahydrofuran.



Scheme 1



Scheme 2

To provide a higher lipophilicity, we decided to introduce a halogen into position 3 of the thiophene ring with respect to chemical simplicity (Scheme 2). Whereas electrophilic substitution of chloride **5** was achieved quantitatively by treatment with sulfuryl chloride at 0°C, attempts to substitution with imidazol led to complete decomposition, forcing us to carry out halogenation on the intermediate **7**. Two equivalents of sulfuryl chloride had to be added to complete the reaction which turned out as a necessity as it was not possible to separate product from educt. Excess reagent, on the other hand, led to more decomposition. As a side product, a small amount of the imidazol-chlorinated derivative **12** was isolated; the exact chloro position could only be limited to position 4 or 5 by spectroscopic methods. Hydrolysis of ester **11** by aqueous sodium hydroxide and subsequent acidification finally yielded the target compound **13**.

Experimental

Melting points were measured on a Kofler apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JOEL FX 90Q FT NMR spectrometer (88.55 MHz) in $CDCl_3$ (internal standard: *TMS*, $\delta = 0.00$) or *DMSO*-d_6 (2.50 ppm rel. to internal *TMS*). Abbreviations: Th = thiophene, Im = imidazol, Bz = Benzene. Elemental analyses agreed satisfactorily with the calculated values.

(2-(2-Methyl-2-propoxy)-ethyl)-5-chlorothiophene-2-carboxylate (**1**; $C_{11}H_{15}ClO_3S$)

A solution of 26.0 g (220 mmol) 2-(2-methyl-2-propoxy)-ethanol [5] and 22.2 g (220 mmol) triethylamine in 100 ml abs. *THF* was quickly dropped to 36.2 g (200 mmol) 5-chlorothiophene-2-carboxylic acid chloride [4] and stirred for one hour at room temperature and for 10 minutes at reflux. The solvent was removed *in vacuo*, and the residue was diluted with sat. $NaHCO_3$ solution and extracted with ether. The organic layer was dried over Na_2SO_4, filtered, evaporated, and the residue distilled *in vacuo* to give 42.3 g **1** (80%) as a colourless oil.

B.p.: 90–93°C/0.007 mbar; ^{1}H NMR (δ, $CDCl_3$): 7.40 (d, $^3J = 4.6$ Hz, Th-H3), 6.75 (d, $^3J = 4.6$ Hz, Th-H4), 4.26 (t, $^3J = 5.5$ Hz, 2H, CH_2-CH_2-OC_4H_9), 3.56 (t, $^3J = 5.5$ Hz, 2H, CH_2-CH_2-OC_4H_9), 1.17 (s, 9H, CH_3) ppm.

(2-(2-Methyl-2-propoxy)-ethyl)-5-(2-(2-methyl-2-proxy)-ethoxy)-thiophene-2-carboxylate (**2**; $C_{17}H_{28}O_5S$)

25.1 g (1.04 mmol) NaH were added in small portions to a solution of 124 g (1.04 mol) 2-(2-methyl-2-propoxy)-ethanol [5] in 300 ml abs. *DMF* keeping the temperature below 45°C. After addition of 180 g (690 mmol) **1** the mixture was stirred at 65°C for one hour, cooled to room temperature, neutralized with 19.8 g acetic acid, poured into sat. $NaHCO_3$ solution, and extracted with ether. The organic layer was dried over Na_2SO_4, filtered, and evaporated yielding 209 g **2** which was used without further purification for the next step. Flash chromatography (silica gel KG 60, Bz:Et_2O = 9:1) gave a yield of 65% **2** as a colourless oil.

B.p.: 135–138°C/0.013 mbar; ^{1}H NMR (δ, $CDCl_3$): 7.41 (d, $^3J = 4.7$ Hz, Th-H3), 6.16 (d, $^3J = 4.7$ Hz, Th-H4), 4.37–3.99 (m, 4H, CH_2-CH_2-OC_4H_9), 3.77–3.45 (m, 4H, CH_2-CH_2-OC_4H_9), 1.17 (s, 18H, CH_3) ppm.

Methyl-5-(2-(2-methyl-2-propoxy)-ethoxy)-thiophene-2-carboxylate (**3**; $C_{12}H_{18}O_4S$)

A solution of 151 g (438 mmol) **2** (or 204 g of raw product from above) and 11.8 g (219 mmol) $NaOCH_3$ in 500 ml abs. CH_3OH was stirred at reflux for one hour. After cooling and addition of

13.2 g (219 mmol) CH_3COOH, the solvent was distilled off, and the residue was diluted with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, evaporated, and distilled *in vacuo* yielding 105 g **3** (93%) as colourless crystals.

B.p.: 139–145°C/0.13 mbar; m.p.: 41–42°C (ligroin); ^{1}H NMR (δ, $CDCl_3$): 7.44 (d, $^3J = 4.6$ Hz, Th-H3), 6.19 (d, $^3J = 4.6$ Hz, Th-H4), 4.14 (t, $^3J = 5.4$ Hz, 2H, C*H*$_2$-CH$_2$-OC$_4$H$_9$), 3.79 (s, OCH_3), 3.67 (t, $^3J = 5.4$ Hz, 2H, CH$_2$-C*H*$_2$-OC$_4$H$_9$), 1.20 (s, 9h, CH_3) ppm.

Methyl-5-(2-hydroxyethoxy)-thiophene-2-carboxylate (**4**; $C_8H_{10}O_4S$)

105 g (410 mmol) **3** were stirred with 100 ml conc. HCl for 15 min, diluted with 100 ml water, and extracted with CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and evaporated yielding 76.0 g **4** (92%) as a colourless oil.

B.p.: 104–107°C/0.013 mbar; ^{1}H NMR (δ, $CDCl_3$): 7.43 (d, $^3J = 4.6$ Hz, Th-H3), 6.19 (d, $^3J = 4.6$ Hz, Th-H4), 4.12 (s, 2H, C*H*$_2$-CH$_2$-OH), 3.96 (s, 2H, CH$_2$-C*H*$_2$-OH), 3.76 (s, OCH_3) ppm.

Methyl-5-(2-chloroethoxy)-thiophene-2-carboxylate (**5**; $C_8H_9ClO_3S$)

29.5 g (248 mmol) $SOCl_2$ were added to a mixture of 45.5 g (225 mmol) **4** and 17.8 g (225 mmol) pyridine in 20 ml abs. $CHCl_3$ under mechanical stirring, keeping the temperature between −40 and −25°C. After raising the temperature to 60°C and stirring for one hour, the mixture was cooled, diluted with water, and extracted with ether. The organic layer was washed with 2 *N* HCl and sat. $NaHCO_3$ solution, dried over Na_2SO_4/charcoal, filtered, and evaporated yielding 76.0 g **5** (92%) as pale yellow crystals.

M.p.: 54–55°C (ligroin) ^{1}H NMR (δ, $CDCl_3$): 7.46 (d, $^3J = 4.6$ Hz, Th-H3), 6.22 (d, $^3J = 4.6$ Hz, Th-H4), 4.29 (t, $^3J = 5.4$ Hz, 2H, C*H*$_2$-CH$_2$-Cl), 3.92–3.55 (m, 5H, C*H*$_2$-CH$_2$-Cl, OCH_3) ppm.

Bis-(2-(2-chloroethoxy)-5-methyoxycarbonyl-3-thienyl)-sulfide (**6**; $C_{16}H_{16}Cl_2O_6S_3$)

3.28 g (27.5 mmol) $SOCl_2$ were rapidly added to a mixture of 5.06 g (25.0 mmol) **4** and 1.98 g (25.0 mmol) pyridine without cooling so that the temperature rose to 60°C. After stirring for one hour at 60°C the mixture was cooled, diluted with water, and extracted with ether. The organic layer was washed with 2 *N* HCl and sat. $NaHCO_3$ solution, dried over Na_2SO_4/charcoal, filtered, and evaporated. Flash chromatography of the residue (silica gel KG 60, Bz) gave 1.40 g **4** (25%) and 1.30 g **6** (22%) as colourless crystals.

M.p.: 145–147°C (acetone) ^{1}H NMR (δ, $CDCl_3$): 7.53 (s, 2H, Th-H), 4.40 (t, $^3J = 5.4$ Hz, 4H, C*H*$_2$-CH$_2$-Cl) 3.91–3.64 (m, 10H, C*H*$_2$-CH$_2$-Cl, OCH_3) ppm.

Methyl-5-(2-(1-imidazolyl)-ethoxy)-thiophene-2-carboxylate (**7**; $C_{11}H_{12}N_2O_3S$)

A mixture of 2.25 g (33 mmol) imidazol and 0.79 g (33 mmol) NaH in 20 ml abs. *DMF* was heated to 90°C until evolution of hydrogen stopped. After cooling and addition of 6.60 g (30 mmol) **5** and 0.22 g (1.5 mmol) NaI in 10 ml abs. *DMF*, the mixture was heated at 70°C for one hour. The solvent was distilled off, the residue diluted with ether and extracted with 2 *N* HCl. The aqueous layer was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated yielding 4.00 g **7** (53%) as colourless crystals.

M.p.: 93–95°C (benzene); ^{1}H NMR (δ, $CDCl_3$): 7.50 (s, Im-H2), 7.43 (d, $^3J = 4.7$ Hz, Th-H3), 7.02 (s, Im-H4*), 6.97 (s, Im-H5*), 6.17 (d, $^3J = 4.7$ Hz, Th-H4), 4.31 (s, 4H, CH$_2$-CH$_2$-Im), 3.81 (s, OCH_3) ppm.

Methyl-5-ethenoxythiophene-2-carboxylate (**8**; $C_8H_8O_3S$)

Evaporation of the ether layer of **7** and purification by flash chromatography (silica gel KG 60, Bz) afforded 1.54 g **8** (28%) as a colourless oil.

B.p.: 130–134°C/13 mbar; ^{1}H NMR (δ, $CDCl_3$): 7.42 (d, $^3J = 4.6$ Hz, Th-H3), 6.32 (dm $^3J = 4.6$ Hz, Th-H4), ABX-system: 4.53 (dd, 1H, CH=CH_{2a}), 4.87 (dd, 1H, CH=CH_{2b}), 6.55 (dd, C*H*=CH_2), $^3J_{AB} = 2.8$ Hz, $^3J_{AX} = 6.2$ Hz, $^3J_{BX} = 14.0$ Hz, 3.78 (s, OCH_3) ppm.

5-(2-(1-Imidazolyl)-ethoxy)-thiophene-2-carboxylic acid hydrochloride (**9**; $C_{10}H_{11}ClN_2O_3S$)

A mixture of 2.52 g (10 mmol) **7** and 0.48 g (12 mmol) NaOH in 50 ml H_2O was stirred for 3 h. The solvent was distilled off *in vacuo*, the residue acidified with 10 ml 2 *N* HCl, evaporated *in vacuo*, and the remaining water was distilled twice aceotropically with benzene. For separating from NaCl, the dry residue was triturated twice with 50 ml boiling abs. ethanol. The product was precipitated from the ethanol layer by adding abs. *THF* and filtered, yielding 2.18 g **9** (80%) as colourless crystals.

M.p.: 164–166°C; ^{1}H NMR (δ, *DMSO*-d_6): 11.48 (br s, 2H, COOH, Im · HCl), 9.19 (s, Im-H2), 7.86 (s, Im-H4*), 7.65 (s, Im-H5*), 7.45 (d, $^3J = 4.6$ Hz, Th-H3), 6.48 (d, $^3J = 4.6$ Hz, Th-H4), 4.68 (s, 4H, CH_2-CH_2-Im) ppm.

Methyl-4-chloro-5-(2-chloroethoxy)-thiophene-2-carboxylate (**10**; $C_8H_8Cl_2O_3S$)

2.02 g (15 mmol) SO_2Cl_2 were added to a solution of 2.21 g (10 mmol) **5** in 30 ml abs. $CHCl_3$ at 0°C and stirred for 12 h at room temperature. The mixture was diluted with water, extracted with ether, and the extract was washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and evaporated yielding 2.56 g **10** (99%) as colourless crystals.

M.p.: 55–56°C (ligroin); ^{1}H NMR (δ, $CDCl_3$): 7.43 (s, Th-H), 4.38 (t, $^3J = 5.4$ Hz, 2H, CH_2-CH_2-Cl), 3.90–3.63 (m, 5h, CH_2-CH_2-Cl, OCH_3) ppm.

Methyl-4-chloro-5-(2-(1-imidazolyl)-ethoxy)-thiophene-2-carboxylate (**11**; $C_{11}H_{11}ClN_2O_3S$)

0.16 g (1.2 mmol) SO_2Cl_2 were added to a solution of 0.15 g (0.59 mmol) **7** in 5 ml abs. $CHCl_3$ at −40°C, stirred for 12 h without cooling, poured into 2 *N* HCl, and washed with ether. The aqueous layer was neutralized with $NaHCO_3$, extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4, filtered, and evaporated. Flash chromatography of the residue (silica gel KG 60, Bz: EtOH = 9:1) gave 73 mg **11** (43%) as pale brown crystals.

M.p.: 97–99°C; ^{1}H NMR (δ, $CDCl_3$): 7.51 (s, Im-H2), 7.37 (s, Th-H), 7.00 (s, 2H, Im-H4,5), 4.34 (s, 4H, CH_2-CH_2-Im), 3.80 (s, OCH_3) ppm.

Methyl-4-chloro-5-(2-(chloro-1-imidazolyl)-ethoxy)thiophene-2-carboxylate (**12**; $C_{11}H_{10}Cl_2N_2O_3S$)

Preparation of **11** yielded 15 mg by-product **12** (2%) as pale brown crystals.

M.p.: 108–110°C; ^{1}H NMR (δ, $CDCl_3$): 7.57 (s, Im-H2), 7.37 (s, Th-H), 6.89 (s, Im-H), 4.34 (s, 4H, CH_2-CH_2-Im), 3.79 (s, OCH_3) ppm.

4-Chloro-5-(2-(1-imidazolyl)-ethoxy)-thiophene-2-carboxylic acid hydrochloride (**13**, $C_{10}H_{10}Cl_2N_2O_3S$)

A mixture of 3.50 g (12.2 mmol) **11** and 0.54 g (13.4 mmol) NaOH in 50 ml water was stirred for 3 h. The solvent was distilled off *in vacuo*; the residue was acidified with 15 ml 2 *N* HCl, evaporated *in vacuo*, and remaining H_2O was distilled twice aceotropically with benzene. For separating from

NaCl, the dry residue was triturated with boiling abs. ethanol. The solution was evaporated and the residue recrystallized from ethanol yielding 2.94 g **13** (78%) as beige crystals.

M.p.: 220°C (ethanol, decomp.); ^{1}H NMR (δ, *DMSO*-d_6): 11.12 (br s, 2H, COOH, Im · HCl), 9.05 (s, Im-H2), 8.02 (s, Im-H4*), 7.85 (s, Im-H5*), 7.61 (s, Th-H), 4.62 (s, 4H, CH_2-CH_2-Im) ppm.

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