3,5-Dihydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-Dioxide – A New Simple Pyrrole Unit

Preliminary Communication

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Dedicated to Professor *Klaus Müller*, Basel

2,3-Dihydrothiophene 1,1-dioxide ('2-sulfolene') reacted with tosylmethyl isocyanide (TsMIC) in the presence of a base to give the hitherto unknown 3,5-dihydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide ('β'-sulfolenopyrrole') from the expected cyclocondensation. A serendipitous formation of this β'-sulfolenopyrrole was found earlier, when we investigated synthetic routes to a 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (a 'β''-sulfolenopyrrole') from TsMIC and 2,5-dihydrothiophene 1,1-dioxide ('3-sulfolene'). Here, we present the synthesis and characterization of β'-sulfolenopyrrole. The X-ray crystal-structure analyses of β'-sulfolenopyrrole and the isomeric β''-sulfolenopyrrole are also reported here. This β'-sulfolenopyrrole is a new type of a functionalized pyrrole, which is likely to be of interest for pharmaceutical purposes.

Introduction. – Pyrroles are the building blocks of porphyrins, chlorins, and other tetrapyrrolic compounds, which are the core moieties of the physiologically important 'pigments of life' [1–4]. The synthesis of pyrroles, their chemistry, and their further use in the production of various materials have received considerable interest [5–8]. Apart from classical pyrrole syntheses, such as the *Paal–Knorr* synthesis [9][10], a variety of other important methods have been developed [11–14]. We were interested in employing cyclocondensation reactions, in particular by the so-called '[3+2]-approach' [15] which provides access to various 2,3,4-substituted pyrroles [8][15–17]. For example, *van Leusen* and co-workers [18–20] reported the reaction of tosylmethyl isocyanide (TsMIC) and α,β-unsaturated ketones/esters (*Michael* acceptors; *Scheme 1*, *a*) for the preparation of 3,4-disubstituted pyrroles [21–24]. Similarly, alkyl α-isocyano esters and nitro-olefins can be reacted using the robust *Barton–Zard* protocol, to produce various substituted pyrroles (*Scheme 1*, *b*) [25] subsequently used in the assembly of porphyrinoid compounds [26–28].

A rational synthesis of functionalized porphyrinoid compounds *via* the reactive tetra-β''-sulfolenoporphyrin **1** [29–31] required the synthesis of the β''-sulfolenopyrrole **2** [32–34] as a building block (*Scheme 2*). Several multi-step sequences for the

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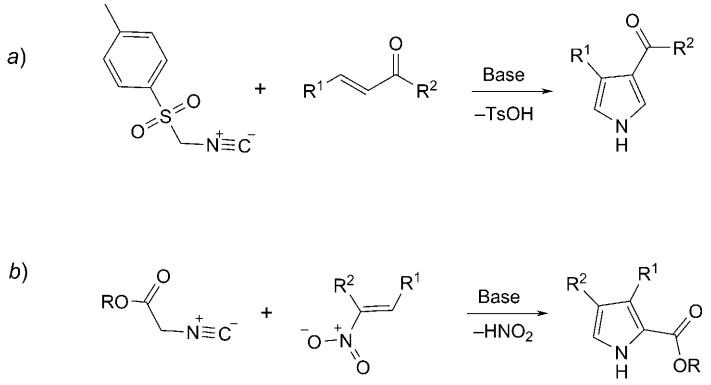
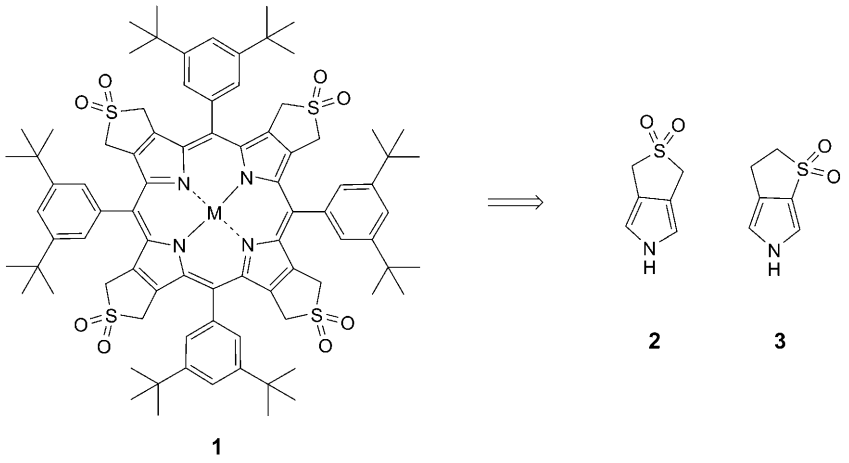
Scheme 1. *Two Examples of the '(3+2)-Approach' to Pyrroles:* a) *TsMIC-Based Approach* [18], b) *α-Isocyano Ester-Based Strategy* [25]



synthesis of **2** have been developed [30][35][36]. However, an interest to improve the overall yield[2]) prompted us to look for more efficient alternative methods to prepare the pyrrole **2**.

Scheme 2. *Structures of Tetra-β″-sulfolenoporphyrin* **1**, *and of Its Precursors β″-Sulfolenopyrrole* **2**, *and of β′-Sulfolenopyrrole* **3**

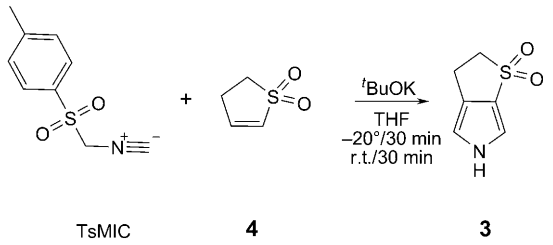


Results and Discussion. In the course of a search for alternative methods for **2**, combining *van Leusen* method with the *Barton–Zard* approach, cyclocondensation

[2]) Benzyl *β″*-sulfolenopyrrole-2-carboxylate was prepared in up to 60% yield by treating benzyl isocyanoacetate with *α,β*-unsaturated sulfones in the presence of a base [35]. However, the acid-catalyzed decarboxylation of the *β″*-sulfolenopyrrole-2-carboxylic acid to give **2** proved to be problematic. The conditions used earlier for decarboxylation (hot CF_3COOH) gave **2** in up to 56% yield [30].

reaction of TsMIC with the α,β-unsaturated '2-sulfolene' (=2,3-dihydrothiophene 1,1-dioxide; as electron deficient *Michael* acceptor) was to be explored. The effectiveness of the reaction was tested with the readily accessible 2-sulfolene **4** (*Scheme 3*), which was prepared *via* base-catalyzed isomerisation of '3-sulfolene' (=2,5-dihydrothiophene 1,1-dioxide; **5**) [37].

Scheme 3. *Cyclocondensation of TsMIC with 2-Sulfolene gives β′-Sulfolenopyrrole* **3**.



The mixture of **4** and TsMIC in THF was added to a suspension of ^{t}BuOK in THF at $-20°$, warmed up to room temperature, and stirred for additional 30 min. The reaction progress was monitored by TLC; the formation of **3** was identified by the characteristic blue stain with *Ehrlich*'s reagent. Aqueous workup and chromatographic purification gave up to 63% of 3,5-dihydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide (**3**; the conventional non-IUPAC numbering is shown in *Fig. 1*). Change of the addition sequence, such as the addition of TsMIC (in THF) to the mixture of **4** and ^{t}BuOK (in THF) at $-20°$, or the addition of **4** to the mixture of TsMIC and ^{t}BuOK (in THF) at $-20°$ gave lower yields (*ca.* 40%) of **3**.

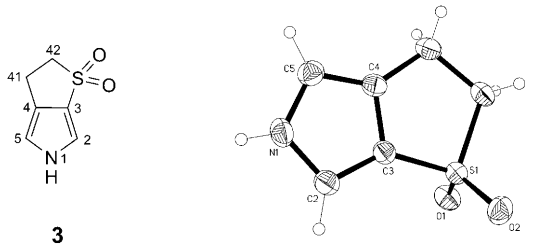


Fig. 1. *X-Ray crystal structure of β′-sulfolenopyrrole* **3**.

Mass-spectrometric analysis of the pyrrole **3** showed the molecular ion ($[M+H]^+$ as base peak) at *m*/*z* 158.0 Da, corresponding to the molecular formula $C_6H_8NO_2S^+$, and little fragmentation. A 300-MHz ^{1}H-NMR spectrum of **3** (in (D_6)acetone) showed two signals of pyrrole H-atoms, at 6.69 (H–C(5)) and 7.15 ppm (H–C(2)), consistent with an unsymmetrical substitution pattern (see *Exper. Part*). The constitution of **3** was established by heteronuclear ^{1}H,^{13}C coupling. The β''-sulfolenopyrrole **2** showed the spectrum of a symmetrical pyrrole: in CD_3OD the two pyrrolic H-atoms gave a signal at 6.75 ppm [32].

The structure of **3** was established by its single-crystal X-ray structure (*Fig. 1*)[3]). The N(1)–C(2) bond (1.354(3) Å) is slightly shorter than the N(1)–C(5) bond (1.365(3) Å), whereas the C(2)–C(3) bond (1.376(3) Å) is a little longer than C(4)–C(5) bond (1.366(3) Å), as rationalized by the electron-withdrawing effect of the SO_2 group. The C(3)–C(4) bond is 1.411(3) Å long. The bond lengths in **2** are 1.362(2) (N(1)–C(2)), 1.369(2) (C(2)–C(3)), and 1.421(2) Å (C(3)–C(4)), respectively (*Fig. 2*). The pyrrol **2** [30] was crystallized by slow evaporation of its MeOH solution.

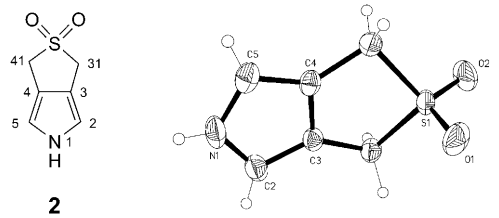
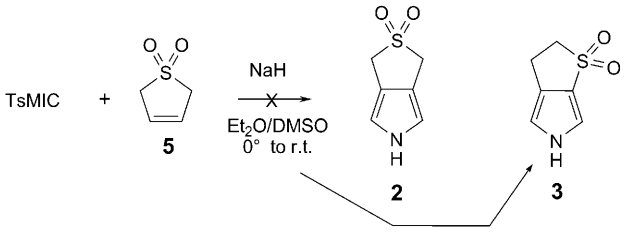


Fig. 2. *X-Ray crystal structure of β″-sulfolenopyrrole* **2**.

As the anion derived from TsMIC is very reactive in cyclocondensation reaction with electron-deficient alkenes [20], 3-sulfolene (**5**) was also tested for its tendency to react with TsMIC. To the suspension of NaH in Et_2O at 0°, a mixture of TsMIC and **5** in DMSO/Et_2O was added. Aqueous workup and chromatographic purification yielded the *β′*-sulfolenopyrrole **3** (instead of **2**) in low (up to 32%) yield (*Scheme 4*), and no trace of the isomeric **2** was found. Change of the addition of the reagents, *i.e.*, first deprotonating TsMIC with NaH and then adding **5**, did not yield any **2** but only **3**.

Scheme 4. *Cyclocondensation of TsMIC with 3-Sulfolene.*



The formation of **3** (under these conditions) can be explained as follows: the 3-sulfolene **5** is a poor reactant in the cyclocondensation reaction with the anion of TsMIC. Deprotonation of **5** at the CH_2(2) group (adjacent to the sulfone function) and *in-situ* reprotonation at the 4-position leads to the 2-sulfolene **4** faster than nucleophilic attack of the anion of TsMIC on **5** could take place (*Scheme 4*). Indeed, alkylation of the anion derived from deprotonation of the 3-sulfolene **5** with NaH/DMF, was observed to lead to the formation of a mixture of the 2-alkyl-2-sulfolene and 2-alkyl-3-sulfolene, in a 1:3 to 1:1 ratio, depending on the alkylating agent used [38].

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[3]) CCDC-748499 and CCDC-748498 contain the supplementary crystallographic data for **3** and **2**, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

Conclusions. – We reported herein a cyclocondensation reaction between the 2-sulfolene **4** and the anion of TsMIC, which provided efficient access to the β'-sulfolenopyrrole **3**. To the best of our knowledge **3** is a new compound. Modifications introduced in the assembly, such as α-substituted TsMIC [39], 4- or 5-substituted 2-sulfolenes [38], would generate substituted β'-sulfolenopyrroles under similar reaction conditions.

The conjugated sulfolene functionality is expected to modulate the reactivity of the pyrrole moiety in a predictable fashion. The β'-sulfolenopyrrole **3** thus has fine-tuned electronic properties and an interesting reactivity for further exploitation, which could assist in selective functionalization at C(2) and C(5). It may thus be of interest for further synthetic transformations, *e.g.*, for further assembly (to porphyrinoid compounds), as well as a basic unit, to be explored for pharmaceutical purposes.

Experimental Part

General. Tosylmethyl isocyanide (TsMIC), 3-sulfolene, NaH, ^{t}BuOK, abs. DMSO were from *Fluka*, abs. THF from *Acros*, and they were used as received. CH_2Cl_2, AcOEt, petroleum ether (PE 40–60), and Et_2O were from *Acros* and were distilled before use. Glassware for all reactions was oven-dried at 110° and cooled under N_2 flow prior to use. Column chromatography (CC): *Fluka* silica gel 60 (230–400 mesh). High vacuum: *ca.* 0.05 mbar. ^{1}H- and ^{13}C-NMR spectra: *Bruker* (^{1}H: 300 MHz, ^{13}C: 75 MHz) at 300 K; chemical shifts δ in ppm, J in Hz, with $\delta(CHD_2COCD_3)$ 2.05 ppm, $\delta(CD_3COCD_3)$ 29.9 and 206.7 ppm. FAB-MS: *Finnigan MAT-95*, positive-ion mode, glycerine matrix; *m*/*z* (rel. intensity %).

*3,5-Dihydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-Dioxide* (**3**). To the suspension of 230 mg of ^{t}BuOK (2 mmol, 2 equiv.) in 7 ml of dry THF at −20°, a soln. of 195 mg of TsMIC (1 mmol, 1 equiv.) and 135 mg of *2,3-dihydrothiophene 1,1-dioxide* (**4**; 1.15 mmol, 1.1 equiv.) in 10 ml of dry THF was added dropwise over 15 min with rigorous stirring. The resulting pale yellow suspension was stirred for 20 min at −20° and then left to warm up to r.t., while stirring for another 30 min. The reaction progress was monitored by TLC (CH_2Cl_2/AcOEt 9:1) for the consumption of TsMIC and product formation with *Ehrlich*'s reagent (0.1% 4-(dimethylamino)benzaldehyde in conc. HCl).

To the mixture, 5% aq. Na_2CO_3 (15 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The org. extracts were washed with H_2O (20 ml), dried (Na_2SO_4), filtered, and the solvents were evaporated *in vacuo*. The mixture was purified by CC (15 × 2 cm) with AcOEt/CH_2Cl_2 gradient. The product **3** was dried in high vacuum at 40° overnight to obtain 98.6 mg of crude **3** (0.628 mmol, 63%). The crude **3** was suspended in acetone (1 ml) and precipitated by addition of Et_2O (6 ml). The precipitated product was filtered, dried overnight in high vacuum at 40° to obtain 94.8 mg (0.604 mmol, 60.4%) of **3**. TLC (CH_2Cl_2/AcOEt 9:1): R_f 0.25. M.p. 208–209°. ^{1}H-NMR ((D$_6$)acetone): 3.14 (*t*, J = 6.8, CH_2(41)), 3.61 (*t*, J = 6.8, CH_2(42)), 6.69 (br. *s*, H–C(5)), 7.15 (br. *s*, H–C(2)), 10.80 (br. *s*, NH(1)). ^{1}H-NMR (300 MHz, CD_3OD): 3.17 (*t*, J = 6.5, CH_2(41)), 3.69 (*t*, J = 6.8, CH_2(42)), 6.62 (br. *s*, H–C(5)), 7.09 (br. *s*, H–C(2)). ^{13}C-NMR: (75 MHz): 20.2 (C(41); 59.7 (C(42); 112.2 (C(2)); 112.9 (C(5)); 126.0 (C(4)); 127.4 (C(3)). FAB-MS: 159.0 (11), 158.0 (100, $[M+1]^+$, $C_6H_8NSO_2^+$; calc. 158.02).

Suitable crystals of **3** for X-ray diffraction were obtained from (D$_6$)acetone by slow evaporation of the solvent at r.t.

Crystal Data and Details of Structure Refinement for **3**. Crystals were grown from C_2D_6O. Crystals data at 233(2) K for $C_6H_7NO_2S$ (M_r 157.19). Crystal system, monoclinic; space group, $P2_1/n$ (no. 14); a = 6.8399(5), b = 10.5559(8), c = 9.0749(4) Å, α = 90°, β = 99.479(4)°, γ = 90°; V = 646.27(7) Å^3. θ Range for data collection, 2.98–24.99°; wavelength 0.71073 Å. Z, 4; density (calc.), 1.616 g/cm^3; absorption coefficient, 0.427 mm^{-1}; F(000), 328; crystal size 0.28 × 0.1 × 0.06 mm^3; index ranges, $-8 \le h \le 7$, $-12 \le k \le 11$, $-10 \le l \le 10$; reflections collected, 3215; independent reflections, 1131 [R_{int} = 0.0229]; reflections [$I > 2\sigma(I)$], 1007; completeness to θ = 24.99° 99.4%; absorption correction: none. Refinement method: full-matrix least-squares on F^2, data/restraints/parameters 1131/0/96; goodness-of-fit on F^2 1.089; final R

indices [$I > 2\sigma(I)$], $R_1 = 0.0315$, $wR_2 = 0.0750$; R indices (all data), $R_1 = 0.0364$, $wR_2 = 0.0774$; extinction coefficient, 0.008(4); largest diff. peak and hole, 0.251 and -0.369 e Å^{-3}. CCDC-748499.

Compound **3** *from the Reaction of 3-Sulfolene* (**5**) *with TsMIC.* To the suspension of 132 mg of NaH (*ca.* 55% in mineral oil, 2.75 mmol, 2.4 equiv.) in 5 ml of dry Et_2O at 0°, a soln. of 227 mg of TsMIC (1.16 mmol, 1 equiv.) and 275 mg of **5** (2.32 mmol, 2 equiv.) in 15 ml of dry Et_2O/abs. DMSO (2:1) was added. After 30 min, consumption of TsMIC and pyrrolic product (R_f 0.25) formation were observed by TLC (CH_2Cl_2/AcOEt 9:1). The mixture was worked up similarly, and CC gave 58.3 mg (0.37 mmol, 32%) of **3** after drying in high vacuum at 40°. The anal. data were identical to those given above for **3**.

X-Ray Structure Analysis of **2**. The β''-sulfolenopyrrole **2** was synthesized according to the reported procedure [30]. Suitable crystals of **2** for X-ray diffraction were obtained from methanol by slow evaporation of the solvent at r.t.

Crystal Data and Details of Structure Refinement for **2**. Crystals were grown from MeOH. Crystals data at 233(2) K for $C_6H_7NO_2S$, (M_r 157.19). Crystal system, orthorhombic; space group, *Pbca* (no. 61); unit cell dimensions, $a = 9.6000(2)$, $b = 9.4868(2)$, $c = 14.6556(4)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; $V = 1334.73(5)$ Å^3; wavelength 0.71073 Å Z, 8; density (calc.), 1.564 g/cm^3; absorption coefficient, 0.414 mm^{-1}; $F(000)$, 656; crystal size, $0.35 \times 0.15 \times 0.15$ mm^3; θ range for data collection, 2.78–27.00°; index ranges, $-12 \le h \le 0$, $-12 \le k \le 12$, $-18 \le l \le 18$; reflections collected, 7852; independent reflections, 1449 [$R_{int} = 0.0222$]; reflections [$I > 2\sigma(I)$], 1345; completeness to $\theta = 27.00°$ 99.5%; absorption correction, none. Refinement method full-matrix least-squares on F^2; data/restraints/parameters, 1449/0/96; goodness-of-fit on F^2, 1.069; final R indices [$I > 2\sigma(I)$], $R_1 = 0.0295$, $wR_2 = 0.0850$; R indices (all data), $R_1 = 0.0318$, $wR_2 = 0.0865$; extinction coefficient, 0.005(3); largest diff. peak and hole, 0.301 and -0.299 e Å^{-3}. CCDC-748498.

We would like to thank Prof. *Karl-Hans Ongania* for mass-spectrometric analysis, the *Austrian Science Foundation* (FWF, project No. P17437 to *B. K.*) for financial support. Dr. *Luke Green* (*F. Hoffmann La Roche*, Basel) is acknowledged for proof-reading this manuscript.

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Received October 13, 2009