Unexpected ring-opening of 2,3-dihydropyridines

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Abstract
The reaction of 2,3-dihydropyridines with sulfonyl halides surprisingly yielded open chain dienes with sulfonylimine structure. The products were specific out of several possible isomers and, therefore, a separation of isomers was not necessary. All new compounds were characterized using FT-IR spectroscopy, HRMS, and NMR spectroscopy. A bicyclic by-product from the reaction of a 2,3-dihydropyridine with mesyl chloride was isolated and its structure elucidated using a single X-ray crystal analysis. Some biological activities, like antimicrobial and cytotoxic properties were investigated.

Graphic abstract

Keywords Sulfonylimines · Dienes · X-ray structure determination · Heterocycles · Structure elucidation · NMR spectroscopy

Introduction

Sulfonylimines have been described recently as important reagents and intermediates for the syntheses of heterocycles [1–3], heterocyclic arrangements [4], cycloadditions [5, 6] and asymmetric Friedel-Crafts reactions [7] as well as for the synthesis of natural products [8, 9]. They were investigated for their antimicrobial [10, 11], herbicidal [12, 13], and anticancer [14] activities.

We already described some reactions of 2,3-dihydropyridines like benzylation in ring positions 1 and 3 [15–17] as well as the reaction with benzoyl halides to acyl derivatives [18] and investigated the antiprotozoal, antimicrobial, and anticancer potencies of these products [15–18]. It seems that the conjugated double bond system and a nitrogen in position 4 are important for those activities, since reduction of the double bonds to a piperidine-4-amine [16] or the hydrolysis to a keto group resulted in a complete loss of activity. To investigate how the electron density in the conjugated system influences the biological activities, we tried to connect the electron withdrawing sulfonyl group to the ring nitrogen by reaction of sulfonyl halides with 2,3-dihydropyridines. Surprisingly, the ring was cleaved and open chain sulfonylimines with diene structure were formed.
Results and discussion

Starting compounds were the bases 1a–1d of 6-unsubstituted tetrahydropyridin-4-ylidene ammonium salts (THPS) which were prepared from their 6-methylsulfanyl analogues via selective reduction with deactivated Raney nickel [19]. During the reaction of compounds 1a–1d with alkane- or arenesulfonyl chlorides a ring cleavage occurred. If an acid scavenger like triethylamine (TEA) was used, the sulfonylimino enamines 2a–5b were obtained, in the absence of an auxiliary base their hydrochlorides 6c–7c were isolated (Scheme 1).

As a mechanism of the ring cleavage, we assume a nucleophilic attack of the ring nitrogen at the sulfur of the sulfonyl halide. Subsequently one of the acidic protons in ring position 3 is removed by the auxiliary base or unreacted starting material. The formation of a new bond between ring atoms 2 and 3 and the cleavage between ring atom 2 and the ring nitrogen should occur simultaneously. Finally, the hydrochloride is given in acidic medium (Scheme 2).

The $\text{E}$-configuration at the double bond between C-2 and C-3 was proven by NMR spectroscopy: A cross-peak was found in a ROESY experiment between the $\text{NCH}_2$ groups of the piperidine ring of compound 4c and the protons in positions 2 and 4 indicating through space interactions between these protons (Fig. 1).

To investigate if lower reaction temperatures avoids the ring opening, we conducted the reaction of 1b with benzene sulfonyl chloride at $-70$ °C (solid CO$_2$/propan-2-ol). At this temperature the 4-chloro compound 8b was mainly formed (Scheme 3).

We investigated, therefore, the course of this reaction at different temperatures with the result, that by trend, the formation of 2b predominated at temperatures from $-21$ to $-1$.
20 °C, whereas its 4-chloro analogue 8b was formed as main product at very low temperatures like −66 °C and −70 °C (Table 1).

The contrast of the yields determined using 1H NMR spectroscopy to the isolated yields is a result of extensive cleaning procedures including repeated purification using CC as well as repeated crystallization. Only pure fractions were considered for the calculation of yields in the experimental part. Mixed fractions as well as mother liquors were not further separated.

During the attempts to form a hydrochloride of 2b, an isomerization of the double bond system to 9b was observed. Due to this positional change of the double bond we observed the following shifts of signals in 13C NMR spectra of 9b compared to the hydrochlorides 6c, 7b, and 7c: the signals of C-3 and C-5 were shifted 3–4 ppm down-field, whereas, the resonance of C-1 shifted 17 ppm to lower frequencies. Furthermore, we observed a separation of the NCH2 signals in 1H NMR spectra due to the loss of rotatability caused by the formed double bond (Fig. 2).

The Z-configuration of the double bond in position 1 of compound 9b was confirmed by NOE-measurements. NOEs where observed between H-1 and H-2 as well as between H-2 and a proton of the NCH2 group of the pyrrolidine ring. Furthermore H-4 and the protons of a methyl group and H-4 and a proton of the other NCH2 group showed through space interactions (Fig. 2). Surprisingly, the bicyclic by-product 10c was isolated as by-product from the reaction of 1c with mesyl chloride. A single X-ray crystal analysis revealed 10c to be (1R,4RS)-6,6-dimethyl-5-(methanesulfonyl)-7-(piperidin-1-yl)-2λ6-thia-5-azabicyclo[2.2.2]oct-7-en-2,2-dione. So far no compounds with a 2-thia-5-azabicyclo[2.2.2]-octane ring system have been published (Fig. 3).

All atoms lie on general positions. The asymmetric unit consists of two molecules (s. Figs. 4, 5) showing very similar geometric parameters.

In addition to the two molecules in 1R,4R configurations there exist two molecules in 1S,4S configurations in the unit cell related by inversion centers (Fig. 6).

Since, as already mentioned, some sulfonylimines showed antimicrobial and anticancer activities, we investigated some of them for their activities against Plasmodium falciparum as well as Trypanosoma brucei rhodesiense, which are the causative organisms of malaria tropica and sleeping sickness, respectively. Moreover, their cytotoxic properties were examined. All of the tested compounds are completely inactive against both parasites. The results are presented in Table 2.

In addition to that, we investigated the anticancer activity of compounds 2a, 2b, 3c, 4c, 7b, and 9b at 5 µM and 50 µM concentration against human leukemia cells (CCRF-CEM). The activities are shown in Fig. 7. The compounds clearly show more inhibitory activity at 50 µM concentration, but their inhibitory potential is low.

The investigation of the activities against some bacteria and yeast was done using drop plate methods. The results are presented in Table 3. Activity against the following
organisms was determined: Bacillus subtilis wild-type 168 (Bac. sub.), Anthrobacter aurescens DSM20116 (Anth. aur.), Escherichia coli K12 (E. coli), Pseudomonas aeruginosa DSM50090 (P. aerug.), and Candida krusei CCMM L10 (Cand. krus.). All of the tested compounds show distinct activity against Anthrobacter aurescens and also potency against the yeast Candida krusei.

Interestingly, compound 9b, the hydrochloride of 2b with shifted double bonds, showed activity against all of the investigated organisms. Especially, the potency against the
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Fig. 6 Unit cell in the crystal of 10c

![Unit cell in the crystal of 10c](image)

Table 2 Antiprotozoal and cytotoxic activities of 7b–10c (IC₅₀ values in µM)

| Cpd | L6 cells | P. falc. NF54 | T. b. rhod |
|-----|----------|--------------|-----------|
|     | IC₅₀<sup>a</sup> | IC₅₀<sup>a</sup> | IC₅₀<sup>a</sup> |
| 7b  | > 250    | 37.9         | 132       |
| 7c  | 207      | 51.3         | 177       |
| 8b  | > 283    | 105          | 173       |
| 9b  | 182      | 48.2         | 282       |
| 10c | 5.31     | 11.4         | 7.36      |
| Mel | 7.78     | 0.0039       |           |
| CQ<sup>c</sup> | 116.9 | 0.007      |           |
| P<sup>d</sup>  | 0.012 |            |           |

<sup>a</sup>Values represent the average of four determinations (two determinations of two independent experiments) indicated in µM

<sup>b</sup>Mel, melarsoprol

<sup>c</sup>CQ, chloroquine diphosphate

<sup>d</sup>P podophyllotoxin

Fig. 7 Anticancer activity of 2a, 2b, 3c, 4c, 7b, and 9b against CCRF-CEM cells as percentages of metabolic active cells compared to the control

![Anticancer activity graph](image)
Gram-negative, aerobic, rod shaped bacterium *Pseudomonas aeruginosa* is noteworthy, since this pathogenic germ is one of the opportunistic pathogens, which is the main cause of prevalent hospital infections worldwide [21].

**Conclusion**

The reaction of 2,3-dihydropyridines yielded unexpected sulfonylimines with diene structure. As a side product, 6-thia-5-azabicyclo[2.2.2]oct-7-en-2,2-dione was isolated whose structure was established with the aid of a single X-ray crystal analysis. The new sulfonylimines were investigated for some antimicrobial and cytotoxic activities. One compound showed distinct activity against *Pseudomonas aeruginosa*. Therefore, further investigations and optimizations of new sulfonylimines will be done to increase the antibacterial activity.

**Experimental**

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200. IR spectra: Bruker Alpha Platinum ATR FT-IR spectrometer (KBr discs). NMR spectra: Bruker Ascend 400, 5 mm tubes, spectra were acquired in CDCl₃ containing 0.03% TMS. Chemical shifts were recorded in parts per million (ppm), for ¹H spectra TMS (0.00 ppm) was used as internal standard and for ¹³C spectra the central peak of the CDCl₃ peak was used as the internal reference (77.0 ppm). Some spectra were acquired in DMSO-d₆. In this case the central peaks of the DMSO-d₆ signal at 2.49 ppm in ¹H spectra and at 39.7 ppm in ¹³C spectra served as internal reference. Abbreviations: aromatic H, ArH; aromatic C, ArC, quaternary aromatic C, ArC₉. Signal multiplicities are abbreviated as follows: s, singlet; d, doublet; dd, doubledoublet; ddd, doubledoubledoublet; dt, doubletriplet; t, triplet; m, multiplet; br, broad. Coupling constants (J) are reported in Hertz (Hz). ¹H and ¹³C resonances were assigned using ¹H,¹H- and ¹H,¹³C-correlation spectra. ¹H and ¹³C resonances are numbered as given in the formulae. HRMS: Micromass tofspec 3E spectrometer (MALDI), GCT-Premier, Waters (EI, 70 eV), Q Exactive Hybrid Quadrupole-Orbitrap mass spectrometer, Thermo Fisher Scientific (HESI, 3.5 kV). Materials: column chromatography (CC): silica gel 60 (Merck 70—230 mesh, pore-diameter 0.6 nm), aluminum oxide (Alox) basic (Fluka for chromatography, 0.05–0.15 mm, Brockmann activity I, basic); Alox neutral 90 (Merck, 0.063–0.2 mm, activity I, neutral); thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F₂₅₄ 0.2 mm, 200×200 mm); TLC plates (Merck, Alox 60 F₂₅₄ neutral, 200×200 mm); the substances were detected in UV light at 254 nm. If no stationary phase is mentioned (CC and TLC) the separation took place using silica gel.

The preparation of the hydroiodides of compounds 1a–1d was already reported by us [19]. The bases were set free by shaking with 2 M NaOH and subsequent extraction with CHCl₃ and used as starting materials without further purification.

**Preparation of compounds 2a–5b**

The bases 1a–1d were co-distilled twice with dry benzene and dissolved in dry dichloromethane. To this solution, dry triethylamine (TEA) and the corresponding arene- or alkane-sulfonyl chloride was added. The reaction mixture was put under an Argon atmosphere and stirred at room temperature. Water was added and the mixture was stirred for 15 min and put into a separatory funnel. The organic layer was separated and the aqueous layer extracted five times with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was evaporated in vacuo and the residue was co-distilled twice with benzene and further purified.
3H, NCH3), 3.06 (s, 3H, NCH3), 5.41 (d, J = 11.1 Hz, 1H, H-2), 5.87 (t, J = 1.5 Hz, 1H, H-4), 7.48–7.58 (m, 3H, ArH), 7.65–7.68 (m, 2H, ArH), 8.10 (d, J = 11.1 Hz, 1H, H-1) ppm; 13C NMR (DSMO-d6, 100 MHz): δ = 20.10 (CH3), 24.99 (CH3), 39.79, 41.44 (2CH3), 96.51 (C-2), 117.34 (C-4), 126.29, 129.14, 131.86 (ArC), 142.65 (ArCq), 143.74 (C-5), 167.81 (C-3), 168.03 (C-1) ppm; IR (KBr): v = 2927, 1558, 1448, 1407, 1344, 1231, 1297, 1284, 1248, 1145, 1086, 891, 804, 725 cm⁻¹; HRMS (EI⁺): m/z calcd. C19H26N2O2S (M⁺) 346.1715, found 346.1714.

**(2E)-N-[5-Methyl-3-(pyrrolidin-1-yl)hexa-2,4-dien-1-ylidene]-benzenesulfonamide (2b, C13H14N2O2S)** Reaction of 553 mg of 1b (3.1 mmol) in 30 cm³ of CH2Cl2 with 548 mg of benzenesulfonic chloride (3.1 mmol) in the presence of 628 mg of TEA (6.2 mmol) yielded after 2 d a residue which was purified by twofold CC using (CH2Cl2:MeOH = 40:1) as eluent. Yield: 95 mg (10%) of 2b as yellow resin. Rf = 0.13 (CH2Cl2:MeOH = 40:1); 1H NMR (DSMO-d6, 400 MHz): δ = 1.51 (d, J = 1.2 Hz, 3H, CH3), 1.77–1.97 (m, 4H, 2CH2), 1.88 (d, J = 1.4 Hz, 3H, CH3), 3.21–3.58 (m, 4H, 2NCH2), 5.30 (d, J = 11.2 Hz, 1H, H-2), 5.91 (t, J = 1.5 Hz, 1H, H-4), 7.47–7.57 (m, 3H, ArH), 7.64–7.69 (m, 2H, ArH), 8.09 (d, J = 11.2 Hz, 1H, H-1) ppm; 13C NMR (DSMO-d6, 100 MHz): δ = 20.20 (CH3), 24.51, 24.77 (2CH2), 25.10 (CH3), 48.79, 50.23 (2NCH2), 97.12 (C-2), 117.75 (C-4), 126.24, 129.12, 131.79 (ArC), 142.83 (ArCq), 143.26 (C-5), 165.02 (C-3), 167.09 (C-1) ppm; IR (KBr): v = 2973, 1558, 1537, 1448, 1352, 1313, 1297, 1283, 1243, 1142, 1085, 885, 805, 791, 725 cm⁻¹; HRMS (EI⁺): m/z calcd. C15H20N2O2S (M⁺) 318.1402, found 318.1437.

**(2E)-N-[5-Methyl-3-(azepan-1-yl)hexa-2,4-dien-1-ylidene]-benzenesulfonamide (2d, C19H22N2O2S)** Reaction of 730 mg of 1d (3.54 mmol) in 31 cm³ of CH2Cl2 with 657 mg of methanesulfonyl chloride (3.1 mmol) in the presence of 1.074 g of TEA (10.6 mmol) yielded after 1 d a residue which was purified by CC using (CH2Cl2:MeOH = 30:1) as eluent. Fractions containing the product were combined, evaporated and the residue recrystallized twice from ethyl acetate/cyclohexane. Yield: 58 mg (5%) of 2d as white needles. Rf = 0.32 (CH2Cl2:MeOH = 30:1); m.p.: 132 °C; 1H NMR (DSMO-d6, 400 MHz): δ = 1.35–1.76 (m, 8H, 4CH2), 1.48 (s, 3H, CH3), 1.88 (s, 3H, CH3), 3.39–3.64 (m, 4H, 2NCH2), 5.46 (d, J = 11.0 Hz, 1H, H-2), 5.92 (s, 1H, H-4), 7.49–7.68 (m, 5H, ArH), 8.10 (d, J = 11.0 Hz, 1H, H-1) ppm; 13C NMR (DSMO-d6, 100 MHz): δ = 20.25 (CH3), 24.98 (CH3), 25.28, 25.55, 26.44, 28.45 (4CH2), 50.22, 52.12 (2NCH2), 96.11 (C-2), 117.16 (C-4), 126.37, 129.19, 131.93 (ArC), 142.53 (ArCq), 143.41 (C-5), 167.17 (C-3), 168.47 (C-1) ppm; IR (KBr): v = 2928, 1551, 1348, 1306, 1283, 1245, 1142, 1084, 875, 791, 766, 725 cm⁻¹; HRMS (EI⁺): m/z calcd. C19H26N2O2S (M⁺) 346.1715, found 346.1714.

**Crystal structure determination of 10c**

All the measurements were performed using monochromatized Mo Kα radiation at 100 K: C19H22N2O2S2, Mf = 348.47, triclinic, space group P-1, a = 8.0619(5) Å, b = 13.2727(9) Å, c = 17.2612(11) Å, α = 69.7412(2)°,
methanesulfonamide (C₁₄H₂₄N₂O₂S)

lengths and angles are deposited at the Cambridge Crystal-

dimensional analyses of molecules are performed by the Cambridge Structural Data Centre (CCDC 206535).

1d (3.59 mmol) in 38 cm³ of CH₂Cl₂ with 432 mg of methanesulfonic acid (3.78 mmol) in the presence of 1.09 g of TEA (10.8 mmol) yielded after 2 d a residue which was purified by CC using CH₂Cl₂:MeOH = 30:1 as eluent. Fractions containing 3d were combined and evaporated. A second CC of the residue over silica gel using (CH₂Cl₂:MeOH = 70:1) followed. Fractions containing the product 3d were combined and evaporated. Yield: 149 mg (15%) of 3d as colorless resin. R₁ = 0.34 (CH₂Cl₂:MeOH = 30:1); ¹H NMR (CDCl₃, 400 MHz): δ = 1.47–1.73 (m, 6H, 3CH₃), 1.68 (d, J = 1.3 Hz, 3H, CH₃), 1.75–1.89 (m, 2H, CH₂), 1.94 (d, J = 1.5 Hz, 3H, CH₃), 2.93 (s, 3H, SO₂CH₃), 3.46–3.58 (m, 4H, 2NCH₂), 5.52 (d, J = 10.8 Hz, 1H, H₂), 5.73 (t, J = 1.4 Hz, 1H, H₄), 8.37 (d, J = 10.8 Hz, 1H, H-1) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ = 20.39 (CH₃), 25.39 (CH₃), 25.64, 25.89, 26.92, 29.12 (4CH₂), 41.20 (SO₂CH₃), 50.54, 52.02 (2NCH₂), 96.42 (C-2), 116.59 (C-4), 144.46 (C-5), 166.45 (C-3), 169.39 (C-1) ppm; IR (KBr): v = 2920, 1553, 1352, 1311, 1293, 1246, 1121, 967, 956, 809, 796 cm⁻¹; HRMS (HESI): m/z calcd. C₁₄H₂₃N₂O₂S⁺ [(M+H⁺)⁺] 285.1637, found 285.1629.

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1246, 1121, 967, 956, 809, 796 cm⁻¹; HRMS (HESI): m/z calcd. C₁₄H₂₃N₂O₂S⁺ [(M+H⁺)⁺] 285.1637, found 285.1629.
30 cm³ of CH₂Cl₂ with 579 mg of benzenesulfonyl chloride (3.28 mmol) yielded after 5 d a residue which was purified by CC using (CH₂Cl₂:MeOH = 20:1) as eluent. Fractions containing 6c were combined and evaporated and the residue subjected to CC with (CH₂Cl₂:MeOH = 9:1) as eluent. Fractions containing only 6c were combined and evaporated and the residue was recrystallized from ethanol/ethyl acetate giving 31 mg of 6c. Impure fractions containing 6c were combined, evaporated and the residue purified using CC with (CH₂Cl₂:MeOH = 9:1) as eluent giving a yellow resin which was recrystallized from ethanol/ethyl acetate and subsequently from ethanol giving additional 35 mg of 6c. Total yield: 66 mg (6%) of 6c as pale orange needles. R_t = 0.78 (CH₂Cl₂:MeOH = 9:1); m.p.: 118 °C (EtOH); ¹H NMR (CDCl₃, 400 MHz): δ = 1.46–1.73 (m, 6H, 3CH₂), 1.62 (s, 3H, CH₃), 1.95 (s, 3H, CH₃), 3.47 (br, s, 4H, 2NCH₂), 5.61 (d, J = 10.8 Hz, 1H, H-2), 5.70 (s, 1H, H-4), 7.41–7.48 (m, 3H, ArH), 7.88 (dd, J = 7.9, 1.7 Hz, 2H, ArH), 8.43 (d, J = 10.8 Hz, 1H, H-1) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ = 20.30 (CH₃), 24.10 (CH₂), 25.42 (CH₂, CH₃), 26.70 (CH₃), 48.02, 50.50 (2NCH₂), 97.37 (C-2), 116.86 (C-4), 126.74, 128.18, 131.52 (ArC), 142.08 (ArCq), 145.16 (C-5), 165.55 (C-3), 169.57 (C-1) ppm; IR (KBr): ν = 2935, 1555, 1445, 1351, 1317, 1282, 1328, 1142, 1086, 1019, 881, 811, 784, 764, 724 cm⁻¹; HRMS (EI⁺): m/z calcd. C₁₈H₂₃N₃O₄S ([M-HCl]⁺) 332.1559, found 332.1564.

(2E)-N-[5-Methyl-1-(4-nitrobenzenesulfonylimino)-hexa-2,4-dien-3-yl]pyrrolidin-1-iium chloride (7c, C₁₈H₂₃CN₃O₄S) Reaction of 547 mg of 1b (3.07 mmol) in 30 cm³ of CH₂Cl₂ with 714 mg of 4-nitrobenzenesulfonyl chloride (3.22 mmol) yielded after 4 d a reaction mixture. Ethyl acetate was added with stirring and the solid was sucked off, washed with ethyl acetate, and purified using CC with (CH₂Cl₂:MeOH = 9:1) as eluent giving a yellow solid. Yield: 262 mg (21%) of 7c. For analytical purposes it was dissolved in CHCl₃, filtered, the solvent evaporated, and the residue recrystallized from ethanol giving yellow needles. R_t = 0.84 (CH₂Cl₂:MeOH = 9:1); m.p.: 183 °C (EtOH); ¹H NMR (CDCl₃, 400 MHz): δ = 1.50–1.74 (m, 6H, 3CH₃), 1.66 (s, 3H, CH₃), 1.99 (s, 3H, CH₃), 3.50–3.53 (m, 4H, 2NCH₂), 5.67 (d, J = 11.0 Hz, 1H, H-2), 5.73 (s, 1H, H-4), 8.05 (d, J = 9.2 Hz, 2H, ArH), 8.28 (d, J = 8.8 Hz, 2H, ArH), 8.41 (d, J = 11.0 Hz, 1H, H-1) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ = 20.89 (CH₃), 23.95 (CH₃), 25.43 (CH₂), 25.50, 26.76 (2CH₂), 48.36, 50.88 (2NCH₂), 97.86 (C-2), 116.49 (C-4), 123.83, 127.82 (ArC), 145.72 (C-5), 148.38, 149.19 (ArCq), 166.66 (C-2), 169.65 (C-1) ppm; IR (KBr): ν = 2940, 1552, 1446, 1349, 1241, 1148, 1085, 889, 817, 782, 739 cm⁻¹; HRMS (EI⁺): m/z calcd. C₁₈H₂₃N₃O₄S ([M-HCl]⁺) 377.1409, found 377.1387; calcd. C₁₈H₂₃N₃O₄S ([M-HCl]⁺) 377.1409, found 377.1387; calcd. C₁₈H₂₃N₃O₄S ([M-HCl]⁺) 377.1409, found 377.1387.

(2E)-N-[4-Chloro-5-methyl-3-(pyrrolidin-1-yl)hexa-2,4-dien-1-ylidene]benzenesulfonamide (8b, C₁₇H₂₃ClN₂O₂S) The reaction of 2.57 g of 1b (14.42 mmol) in 120 cm³ of CH₂Cl₂ with 2.548 g of benzenesulfonyl chloride (14.43 mmol) in the presence of 1.46 g of TEA (14.41 mmol) was started at −70 °C (solid CO₂/2-propanol) and the reaction batch was allowed to come up to room temperature. It was stirred for 2 d. After workup according to the synthesis of 2b a residue was yielded which was purified by treatment with charcoal and subsequent by CC using (CH₂Cl₂:MeOH = 9:1) as eluent giving an orange resin. The slightly impure fractions were combined, evaporated, and the residue recrystallized repeatedly yielding additional product as off-white needles. Yield: 317 mg (6%) of 8b. R_t = 0.12 (CH₂Cl₂:MeOH = 60:1); m.p.: 127 °C; ¹H NMR (CDCl₃, 400 MHz): δ = 1.71 (s, 3H, CH₃), 1.92–2.10 (m, 4H, 2CH₂), 2.00 (s, 3H, CH₃), 3.28–3.40 (m, 3H, NCH₂), 3.57–3.64 (m, 1H, NCH₂), 5.38 (d, J = 10.6 Hz, 1H, H-2), 7.43–7.52 (m, 3H, ArH), 7.88 (dd, J = 8.4, 1.5 Hz, 2H, ArH), 8.38 (d, J = 11.0 Hz, 1H, H-1) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ = 20.71 (CH₃), 21.57 (CH₃), 24.82, 25.04 (2CH₂), 48.68, 49.60 (2NCH₂), 97.36 (C-2), 115.28 (C-2), 126.91, 128.69, 131.88 (ArC), 137.63 (C-5), 141.33 (ArCq), 162.14 (C-3), 167.15 (C-1) ppm; IR (KBr): ν = 2871, 1560, 1448, 1425, 1354, 1320, 1298, 1285, 1243, 1142, 1084, 847, 826, 797, 723 cm⁻¹; HRMS (EI⁺): m/z calcd. C₁₇H₂₃ClN₂O₂S (M⁺) 352.1012, found 352.1035; HRMS (MALDI): m/z calcd.
C17H22ClN2O2S ([M+Na]+) 375.0910, found 375.0934; calcd. C17H22ClN2O2S ([M+H]+) 353.1090, found 353.1066.

(1Z)-1-[1-(Benzenesulfonamido)-5-methylhexa-1,4-dien-3-ylidenepyrolidin-1-ium chloride (9b, C17H22ClN2O2S) Compound 2b (125 mg, 0.39 mmol) was dissolved in CH2Cl2 and treated with an excess of 1.25 M ethanolic HCl (0.63 cm3, 0.78 mmol). The solvent was evaporated in vacuo and the residue was crystallized from ethanol. The first precipitate was filtered with suction, washed with ethanol, and discarded. To the mother liquor diethyl ether was added until crystallization seemed to be complete. The second precipitate was filtered with suction, washed with diethyl ether, and dried in vacuo. Yield: 37 mg (27%) of 9b as white powder. Rf = 0.90 (CH2Cl2:MeOH = 9:1); m.p.: 146 °C; 1H NMR (CDCl3, 400 MHz): δ = 1.60 (s, 3H, CH3), 2.04 (s, 3H, CH3); 2.09–2.17 (m, 4H, 2CH2), 3.74 (br, s, 2H, NCH2), 3.85 (br, s, 2H, NCH2), 5.98 (s, 1H, H-4), 6.80 (d, J = 12.8 Hz, 1H, H-2), 7.53–7.63 (m, 4H, H-1, ArH), 8.02 (d, J = 7.3 Hz, 2H, ArH) ppm; 13C NMR (CDCl3, 100 MHz): δ = 21.09 (CH3), 24.46, 24.64 (2CH2), 25.80 (CH3), 51.78, 53.12 (2NCH2), 101.19 (C-2), 115.85 (C-4), 126.92, 129.33, 133.61 (ArC), 139.25 (ArCq), 148.98 (C-5), 152.23 (C-1), 170.06 (C-3) ppm; IR (KBr): ν = 2957, 1615, 1589, 1446, 1386, 1352, 1243, 1168, 1087, 892, 843, 812, 788, 761, 724 cm–1; HRMS (EI+): m/z calcd. C17H22N2O2S [M-HCl+] 318.1402, found 318.1418.

In vitro antiprotozoal assays and cytotoxicity

The in vitro growth inhibition assay of Plasmodium falciparum NF54 and the in vitro growth inhibition assay of Trypanosoma b. rhodesiense, as well as the assay for the determination of cytotoxicity against L6-cells were performed as described earlier [24].

Cytotoxicity against human CCRF-CEM leukemia cells

The cell culture of CCRF-CEM cells and XTT viability assay were operated as described previously [15].

Detection of antimicrobial activity

Drop plate methods [25] with modification were performed to detect the antimicrobial activity against two Gram-positive strains, two Gram-negative strains, and one yeast strain from accredit source. All compounds were dissolved in DMSO to a concentration of 1 mg/cm3. Using sterile micro-pipette 10 mm3 of each compound was directly but gently dropped over seeded agar plate with test organism. The liquid was allowed to diffuse before the plate was inverted and incubated. The growth conditions for every strain were considered. The results were noted when a lawn of the indicator bacteria appeared on the plate (approximately 10–16 h).

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