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Synthesis of Isoquinoline Alkaloid, (±)-Salsolidine, Using Thiazolino[2,3-*a*]isoquinolinone S-Oxide as Intermediate

by M.D. Rozwadowska* and A. Sulima

Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland

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Thiazolino[2,3-*a*]isoquinolinones have been oxidized to the corresponding S-oxides and their 10b-methyl derivatives desulfurized with Raney nickel to give (±) N-acyl salsolidine. Base-catalyzed hydrolysis of the N-acetyl derivative afforded (±)-salsolidine. C-Methylation reactions of the title heterocyclic system have been investigated throughly. Stereochemistry of the synthesized compounds has been established.

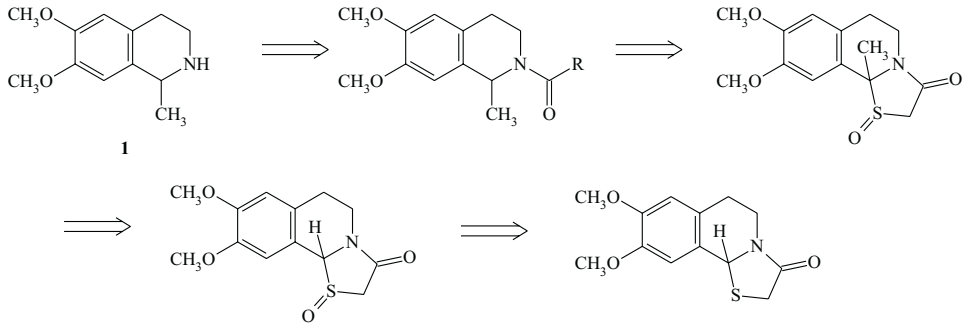
Key words: thiazolino[2,3-*a*]isoquinolinone S-oxide, C-methylation, desulfurization, (±)-salsolidine, isoquinoline alkaloid

Sulfur-mediated synthesis of isoquinoline alkaloids, involving racemic and stereoselective processes, has received increased attention in recent years. In this approach 1,3-dithianes, sulfoxides and sulfoximines have found application both as expedient sources of carbon nucleophiles in C–C bond forming reactions as well as controllers of stereochemistry in diastereoselective synthesis, in which stereogenic sulfur was used for chirality transfer. Thus, 1,3-dithianes in reaction with 3,4-dihydroisoquinoline derivatives, or their synthetic equivalents, have mainly been used for the synthesis of racemic isoquinoline alkaloids [1] and their *seco*- [2] and other analogs [3]. An optically pure 1,3-dithiane was synthesized as well and applied in the synthesis of (+)- and (–)-corydalisol [4]. Several examples of synthesis of chiral non-racemic alkaloids using optically active vinyl-aryl- [5–8] and alkyl-aryl-sulfoxides [9–13] and sulfoximines [14,15] have been reported. In connection with our studies of the synthesis of isoquinoline alkaloids with the use of sulfur-containing intermediates [1,2,4], we turned our attention to thiazolo[2,3-*a*]isoquinoline derivatives, assuming that the corresponding chiral S-oxides would be potential intermediates in asymmetric synthesis, bringing about a 1,2-asymmetric induction.

To test this approach we decided to synthesize a racemic (±)-salsolidine (**1**), a simple isoquinoline alkaloid, often used as target in testing a newly developed synthetic method [16]. The retrosynthetic analysis is shown in Scheme 1.

* Corresponding author. tel.: 48 61 829 13 22; fax.: 48 61 8658 008; e-mail: a.sulima@interia.pl

Scheme 1

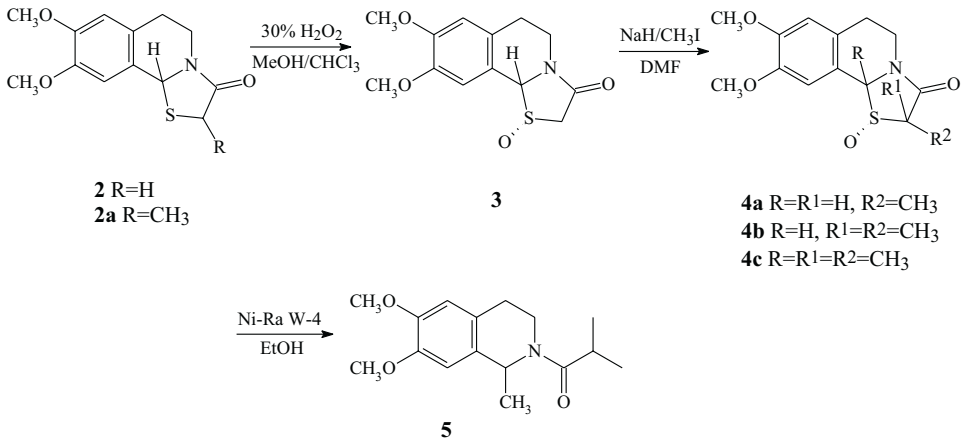


1

RESULTS AND DISCUSSION

In the first experiments, thiazolinoisoquinolinone **2** has been converted into N-acyl salsolidine (**5**) as shown in Scheme 2. Compound **2** [17] was oxidized either with 30% hydrogen peroxide in methanol/water (1:1) or with MCPBA in methylene chloride, to give a mixture of diastereomeric sulfoxides **3**/**3a** in 53 and 58% *d.e.*, respectively. The major isomer **3** was isolated in pure form from crude products mixture by crystallization from methanol/chloroform (1:1), while the second one, **3a**, by extraction of a crude product with carbon tetrachloride. The stereochemistry of **3** was established by X-ray single crystal analysis [18], which proved an *anti* relationship between the newly created stereogenic center at sulfur, with oxygen occupying α position, and H-10b hydrogen on the β side. It should be mentioned that in chloroform solution an equilibrium between **3** and **3a**, at a ratio *ca* 3:1 (NMR), was formed.

Scheme 2



2 R=H
2a R=CH_3

3

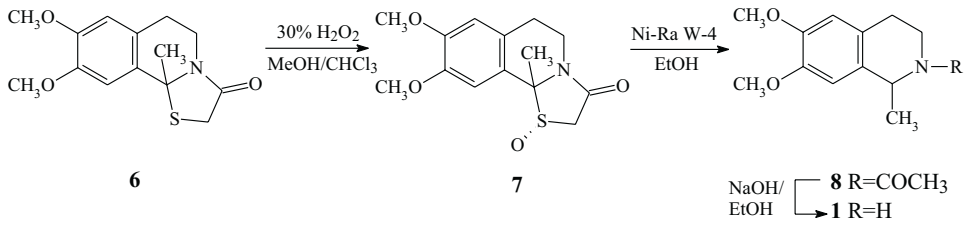
4a R=R1=H, R2=CH_3
4b R=H, R1=R2=CH_3
4c R=R1=R2=CH_3

5

The major isomer **3** was used in the next step of the synthesis. It was C-methylated in the NaH/DMF system with the use of one, two or three molar equivalents of sodium hydride and an excess of methyl iodide to give mono- di- and tri-C-methylated derivatives: **4a**, **b**, **c**, respectively, in good (**4a**, **b**) and moderate (**4c**) yields. As expected, in the presence of more acidic protons in the molecule, the methyl group at the desired 10b position could be introduced at the third step of the methylation. As the result of monomethylation of sulfoxide **3**, a single diastereomer **4a** was obtained, which was also prepared as the major isomer (70% *d.e.*) during S-oxidation of 2-methyl thiazolinoisoquinolinone **2a** [17] with 30% hydrogen peroxide. The stereochemistry of **4a** was deduced from NOE difference experiment, which indicated an interaction between H-10b, H-2 and H-5 axial [17] protons, thus, confirming an α-position of the introduced C-2 methyl group. The second methyl group was also incorporated into the C-2 position, giving **4b** as crystalline compound. Introduction of the third methyl substituent into the C-10b stereogenic center, leading to **4c**, proceeded with retention of configuration. This could be established on the basis of NOE difference measurement, which indicated that the C10b methyl group and the axial H-5 hydrogen [17] in **4c** occupy the same face of the molecule as was the case with the H-10b and H-5 hydrogens in the starting sulfoxide **3**.

Continuing the synthesis of salsolidine (**1**) from **2**, compound **4c** was treated with Raney nickel W-4 [19] in refluxing ethanol to give crystalline N-isobutanoilsalsolidine (**5**) in 55% yield. However, all attempts to hydrolyze the amide function in **5** to give salsolidine (**1**), including reactions catalyzed with different acids and bases carried out under various reaction conditions, have failed. In order to overcome this difficulty another series of experiments has been undertaken, using the known C-10b methyl derivative **6** [17] as the substrate (Scheme 3).

Scheme 3



6 **7**

Oxidation with 30% hydrogen peroxide, as above, produced a mixture of diastereomeric sulfoxides in 96% yield and 25% *d.e*. The more polar (TLC), prevailing isomer **7** was separated from the crude reaction mixture by crystallization from ethanol. Both diastereomers, unlike sulfoxides **3** and **3a**, were found to be quite stable in chloroform solution, as well as in other solvents. Verification of the relative configu-

ration around the stereogenic centers in **7** was made by X-ray single crystal analysis [18]. Like in sulfoxide **3**, the *anti* configuration with α oriented sulfoxide oxygen and β position of the 10b-methyl substituent was proven. Treatment of sulfoxide **7** in refluxing ethanol with Raney nickel W-4 [19] afforded N-acetyl salsolidine **8**, which under the action of concentrated sodium hydroxide at reflux for 5 days was hydrolyzed to the (±)-salsolidine (**1**) in high yield.

Thus, the possibility of conversion of S-oxides of partially reduced thiazolo[2,3-*a*]isoquinoline heterocyclic system into isoquinoline derivatives has been demonstrated by the synthesis of (±)-salsolidine, chosen as a representative. The C-10b methyl derivatives **4c** and **7** were the key intermediates in this approach, which upon desulfurization with Raney nickel W-4 afforded N-acylated salsolidine, **5** and **8**, respectively, from which the later one was hydrolyzed to give the target alkaloid **1**. Stereochemistry of the major S-oxides and the corresponding C-methyl derivatives was also investigated. The above results seem to imply that the use of chiral non-racemic sulfoxides of the thiazolino[2,3-*a*]isoquinolinone heterocyclic system may open a new way to asymmetric synthesis of isoquinoline alkaloids.

EXPERIMENTAL

General: Melting points were determined on a Koffler block and are not corrected. IR spectra were recorded on Perkin-Elmer 180, in KBr pellets. NMR spectra were taken in $CDCl_3$ or DMSO-d_6 on Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.45 MHz), with TMS as internal standard. Mass spectra (EI) and FAB techniques were obtained by using Joel D-100, 75 eV. For FAB-mass spectra, 3-nitrobezyl alcohol was used as a matrix. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography and Merck DC-Alufolien Kieselgel 60_{254} for TLC.

S-Oxidation of thiazolinoisoquinolinones. General procedure: To a solution of thiazolinoisoquinolinone (2 mmol) in methanol/chloroform (2:1), (15 ml) hydrogen peroxide (1.5 ml, 30%) and water (3 ml) were added. The mixture was stirred at room temperature for 2.5–3 h. Solvents were removed, water (5 ml) was added and the mixture extracted with chloroform. The organic extract was dried and the solvent evaporated to give crude sulfoxide.

8,9-Dimethoxy-6,10b-dihydro-1-oxo-5H-thiazolo[2,3-a]isoquinolin-3-one (3): Mixture of diastereomers from **2** [17]; Yield = 75%. *Major isomer* **3** was separated by crystallization of the crude reaction product from methanol/chloroform; Yield = 42%; crystals; m.p. 212–214°C; IR cm^{-1}: 1688; ^{1}H NMR δ ($CDCl_3$): 2.67–2.74 (m, 1H, H-6′), 2.96 (dt, J = 15.0, 12.2, 4.4 Hz, 1H, H-6), 3.09 (dt, J = 12.2, 12.2, 2.6 Hz, 1H$_a$, H-5), 3.72 (ABq, J = 16.5, 10.9 Hz, 2H, H-2α and H-2β), 3.88 and 3.91 (2x s, 6H, 2x OCH_3), 4.55 (ddd, J = 12.2, 4.4, 1.6 Hz, 1H$_e$, H-5), 5.64 (s, 1H, H-10b), 6.70 and 6.79 (2x s, 2H, H-7 and H-10); ^{13}C NMR δ ($CDCl_3$): 28.34 (C-6), 39.54 (C-5), 55.70 (C-2), 76.71 (C-10b), 108.65 and 112.32 (C-7, C-10), 116.44 and 123.38 (C-8, C-9), 130.34 and 148.81 (C-6a, C-10a), 168.04 (C-3); MS m/z (%): 281 (M$^+$, 42), 233 (11), 191 (100), 176 (13); HRMS: calcd. for $C_{13}H_{15}NO_4S$ (M$^+$): 281.07217, found: 281.07239.

Minor isomer **3a** was obtained by extraction of the crude reaction mixture with carbon tetrachloride; Yield = 27%; crystals; m.p. 164–167°C. IR cm^{-1}: 1711; ^{1}H NMR δ (DMSO-d_6): 2.49–2.72 (m, 2H, H-6), 2.97 (dt, J = 10.3, 10.3, 2.1 Hz, 1H$_a$, H-5), 3.75 and 3.77 (2x s, 6H, 2x OCH_3), 3.98 and 4.15 (2x d, J = 14.5 Hz, 2H, H-2), 4.26 (ddd, J = 10.3, 4.3, 1.8 Hz, 1H$_e$, H-5), 5.61 (s, 1H, H-10b), 6.87 and 6.95 (2x s, 2H, H-7 and H-10); ^{13}C NMR δ ($CDCl_3$): 28.03 (C-6), 39.10 (C-5), 55.26 (C-2), 79.08 (C-10b), 108.18 and 111.86 (C-7, C-10), 119.84 and 126.43 (C-8, C-9), 131.00 and 149.55 (C-6a, C-10a), 163.94 (C-3); MS m/z (%): 281 (M$^+$, 44), 233 (22), 191 (100), 176 (41); HRMS: calcd. for $C_{13}H_{15}NO_4S$ (M$^+$): 281.07217, found: 281.07309.

8,9-Dimethoxy-2-methyl-1-oxo-6,10b-dihydro-5H-thiazolo[2,3-a]isoquinolin-3-one (4a): Prepared from diastereomeric mixture of **2a** [17]; Yield = 79%; *major isomer* **4a** was obtained by crystallization of

the crude product from methanol; Yield = 47%; crystals; m.p. 207–209°C; IR cm^{-1}: 1712; ^1H NMR δ ($CDCl_3$): 1.62 (d, J = 7.3 Hz, 3H, CH_3), 2.66–2.70 (m, 1H, H-6′), 2.94 (dt, J = 15.6, 12.6, 5.1 Hz, 1H, H-6), 3.08 (dt, J = 12.6, 12.6, 2.6 Hz, $1H_a$, H-5), 3.62 (q, J = 7.3 Hz, 1H, H-2), 3.88 and 3.91 (2x s, 6H, 2x OCH_3), 4.52 (ddd, J = 12.6, 5.1, 1.4 Hz, $1H_e$, H-5), 5.59 (s, 1H, H-10b), 6.68 and 6.82 (2x s, 2H, H-7 and H-10); ^{13}C NMR δ ($CDCl_3$): 7.32 (CH_3), 28.28 (C-6), 39.60 (C-5), 58.95 (C-2), 74.08 (C-10b), 108.69 and 112.18 (C-7, C-10), 116.46 and 130.21 (C-8, C-9), 148.69 and 149.39 (C-6a, C-10a), 170.39 (C-3); MS m/z (%): 295 (M^+, 31), 247 (36), 219 (12), 191 (100), 176 (32), 28 (23). HRMS: calcd. for $C_{14}H_{17}NO_4S$ (M^+): 295.08783, found: 295.08671.

8,9-Dimethoxy-10b-methyl-1-oxo-6,10b-dihydro-5H-thiazolo[2,3-a]isoquinolin-3-one (7): Prepared from **6** [17] in yield 96%; mixture of diastereomers, *d.e.* 25%; *major isomer* **7** was obtained by crystallization of the crude product from ethanol; crystals; m.p. 198–199°C (lit. [20] 214–216°C hexane/ethyl acetate); IR cm^{-1}: 1675; ^1H NMR δ ($CDCl_3$): 1.73 (s, 3H, CH_3), 2.72 (dt, J = 15.3, 3.2, 1.5 Hz, 1H, H-6′), 3.00 (ddd, J = 15.3, 12.4, 4.9 Hz, 1H, H-6), 3.13 (dt, J = 12.4, 12.4, 3.2 Hz, $1H_a$, H-5), 3.57 and 3.90 (2x d, J = 16.9 Hz, 2H, H-2α and H-2β), 3.87 and 3.91 (2x s, 6H, 2x OCH_3), 4.52 (ddd, J = 12.4, 4.9, 1.5 Hz, $1H_e$, H-5), 6.65 and 6.72 (2x s, 2H, H-7 and H-10); ^{13}C NMR δ ($CDCl_3$): 23.74 (C-10b), 28.46 (C-6), 37.60 (C-5), 53.07 (C-2), 108.65 and 111.95 (C-7, C-10), 122.20 and 129.39 (C-8, C-9), 148.39 and 149.16 (C-6a, C-10a), 166.29 (C-3); MS m/z (%): 295 (M^+, 80), 247 (38), 205 (100), 190 (38); HRMS: calcd. for $C_{14}H_{17}NO_4S$ (M^+): 295.08783, found: 295.09011.

C-Methylation of sulphoxide 3. General procedure: To a solution of sulfoxide **3** (1 mmol) in DMF (6 ml) at 0°C under an argon atmosphere sodium hydride (1.1 mmol for **4a**, 2.2 mmol for **4b** and 3.3 mmol for **4c**) was added and the mixture was kept at this temperature for 30 min. Then excess of CH_3I was added and the suspension stirred at 0°C for 3 h. The mixture was poured onto ice (*ca*. 40 g) and the precipitate (**4a**) was filtered off or the aqueous phase was extracted with dichloromethane (**4b**,**c**). The organic extract was dried and the solvent evaporated to give crude product, which was purified on silica gel column, eluting with dichloromethane.

8,9-Dimethoxy-2-methyl-1-oxo-6,10b-dihydro-5H-thiazolo[2,3-a]isoquinolin-3-one (4a): Obtained as pure diastereomer; Yield 89%, identical with the major isomer prepared by oxidation of **2a**.

8,9-Dimethoxy-2,2-dimethyl-1-oxo-6,10b-dihydro-5H-thiazolo[2,3-a]isoquinolin-3-one (4b): Yield 78%; crystals; m.p. 216–218°C (from methanol); IR cm^{-1}: 1674; ^1H NMR δ ($CDCl_3$): 1.50 and 1.59 (2x s, 6H, 2x CH_3), 2.64–2.70 (m, 1H, H-6′), 2.94 (dt, J = 15.1, 12.2, 4.9 Hz, 1H, H-6), 3.06 (dt, J = 12.2, 12.2, 3.3 Hz, $1H_a$, H-6), 3.87 and 3.91 (2x s, 6H, 2x OCH_3), 4.50 (ddd, J = 12.2, 4.9, 1.6 Hz, $1H_e$, H-5), 5.71 (s, 1H, H-10b), 6.68 and 6.81 (2x s, 2H, H-7 and H-10); FAB MS m/z (%): 310 (M^+, 100), 261 (59), 192 (61); HRMS: calcd. for $C_{15}H_{20}NO_4S$ (M^+): 310.11130, found: 310.11016.

8,9-Dimethoxy-2,2,10b-trimethyl-1-oxo-6,10b-dihydro-5H-thiazolo[2,3-a]isoquinolin-3-one (4c): Yield 59%; crystals; m.p. 158–160°C (from methanol/hexane); IR cm^{-1}: 1679; ^1H NMR δ ($CDCl_3$): 1.41 and 1.50 (2x s, 6H, 2x CH_3), 1.83 (s, 3H, CH_3), 2.63–2.70 (m, 1H, H-6′), 2.90 (dt, J = 16.5, 13.1, 6.3 Hz, 1H, H-6), 3.20 (dt, J = 13.1, 13.1, 4.4 Hz, $1H_a$, H-5), 3.87 and 3.90 (2x s, 6H, 2x OCH_3), 4.52 (ddd, J = 13.1, 6.3, 1.1 Hz, $1H_e$, H-5), 6.58 and 6.83 (2x s, 2H, H-7 and H-10); FAB MS m/z (%): 324 (M^+, 68), 308 (24), 275 (31), 206 (26), 154 (100), 146 (68), 107 (22); HRMS: calcd. for $C_{16}H_{22}NO_4S$ (M^+): 324.12695, found: 324.12622.

Desulfurization of S-oxides. General procedure: Raney nickel W-4 [19] (prepared from Raney nickel-aluminum alloy (23 g)) and sulfoxide (1.2 mmol) in ethanol (30 ml) were stirred under reflux for 15 min. The hot solution was filtered through a pad of Celite and washed with hot ethanol. The solvent was evaporated, the residue was dissolved in dichloromethane and washed with water. The organic phase was dried and the solvent evaporated to give crude product.

6,7-Dimethoxy-2-isobutanoil-1,2,3,4-tetrahydroisoquinoline (5): Prepared from sulfoxide **4c**; Yield 91%; crystals; m.p. 99–100°C (from hexane/ethyl acetate, 3:2); IR cm^{-1}: 1628; ^1H NMR δ ($CDCl_3$): 1.15 and 1.17 (2x d, J = 5.5 Hz, 6H, 2x CH_3), 1.41 (d, J = 6.9 Hz, 3H, CH_3), 2.61–3.05 (m, 3H, H_e-3, 2H-4), 3.47 (ddd, J = 13.5, 11.5, 4.1 Hz, 1H, H_a-3), 3.85 and 3.86 (2x s, 6H, 2x OCH_3), 3.91–3.98 (m, 1H, C*H*(CH_3)$_2$), 5.59 (q, J = 6.9 Hz, 1H, H-1), 6.58 and 6.62 (2x s, 2H, H-5 and H-8); MS m/z (%): 277 (M^+, 28), 262 (68), 192 (100); HRMS: calcd. for $C_{16}H_{23}NO_3$ (M^+): 277.16779, found: 277.16887.

2-Acetyl-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (8): Prepared from sulfoxide **7**; Yield 55%; crystals; m.p. 100–102°C, (from hexane/ethyl acetate), (lit. [21] m.p. 100–101°C, from hexane); IR cm^{-1}: 1634; ^1H NMR δ ($CDCl_3$): 1.43 (d, J = 6.9 Hz, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.61–3.04 (m,

3H, 1H-3 and 2H-4), 3.46–3.55 (m, 1H, H-3), 3.85 and 3.86 (2x s, 6H, 2x OCH_3), 5.58 (q, J = 6.9 Hz, 1H, H-1), 6.59 and 6.72 (2x s, 2H, H-5 and H-8); MS m/z (%): 249 (M^+, 30), 234 (77), 192 (100); HRMS: calcd. for $C_{14}H_{19}NO_3$ (M^+): 249.13638, found: 249.13737.

(±)-Salsolidine (**9**): A solution of N-acetyl salsolidine (**8**) (0.1 g, 0.4 mmol) in ethanol (5 ml) and NaOH (0.8 g) in water (5 ml) was refluxed for 5 days. The alcohol was then removed and the aqueous layer was extracted with dichloromethane. The organic extract was combined, dried and then evaporated to give (±)-salsolidine (**1**) (0.08 g, yield 95%), identical with the alkaloid in terms of spectral data [22] as well as chromatographic (TLC) comparison.

Acknowledgments

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