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# Sulfur ylides

## 11.* Selected chemical transformations of 1-methylthio-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione

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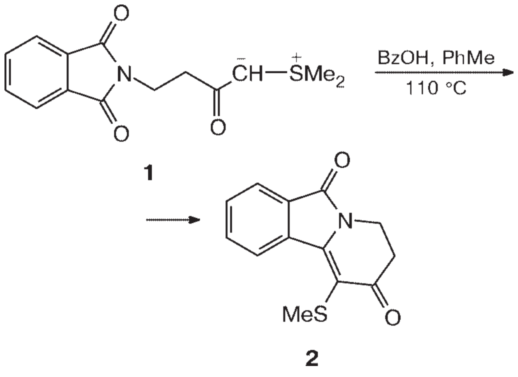
The reaction of 1-methylthio-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione (**2**) with $NaBH_4$ led to reduction of the keto group to the hydroxy group. The reaction with the use of $LiAlH_4$ resulted in complete reduction of the carboximide group, reduction of the keto group to the hydroxy function, and reduction of the double bond accompanied by desulfurization. The reaction of indolizidinedione **2** with Zn afforded a reductive desulfurization product. The reactions of **2** with hydrazine hydrate, hydroxylamine, and formamide proceeded according to a mechanism typical of the keto group to give hydrazone, oxime, and the formyl derivative, respectively. Oxidation of the thiomethyl group of the starting compound with $Bu^tOOH$ gave rise to sulfone or sulfoxide depending on the amount of the oxidizing agent used.

**Key words:** 1-methylthio-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione, reduction, desulfurization, oxidation, intramolecular cyclization.

Previously, we have demonstrated[2] that intramolecular cyclization of keto-stabilized sulfur ylide (**1**) derived from *N*-phthaloyl-β-alanine afforded 1-methylthio-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione (**2**) (Scheme 1). Taking into account that compounds of the indolizidinedione series have the high synthetic potential, it was of interest to study chemical transformations of dione **2**.

**Scheme 1**



### Results and Discussion

Reduction of indolizidinedione **2** with $NaBH_4$ in EtOH afforded unsaturated alcohol **3** (Scheme 2, path *a*), which was confirmed by the fact that the IR spectrum of the product has an absorption band corresponding to the OH group (ν 3400 $cm^{-1}$).

The reaction of compound **2** with $LiAlH_4$ in THF proceeded with reduction of the carbonyl group at the C(2) atom to the hydroxy group, complete reduction of the carboximide group, reduction of the double bond, and elimination of the thiomethyl fragment to form alcohol **4** (see Scheme 2, path *b*). The structure of compound **4** was confirmed by the $^1H$ NMR spectrum in which complete splitting of all protons was observed. The assignment of the signals was made based on the 2D homonuclear experiment using the standard COSY-45 technique, and all correlations between the coupled protons were determined. As a first approximation, the spin-spin coupling constants were determined from the 1D NMR spectrum. From these constants, it is evident that the signal for the proton at the C atom bound to the OH group ($\delta_H$ 3.71) occurs as a triplet of doublets ($J_t$ = 11.4 Hz; $J_d$ = 4.7 Hz), which corresponds to the equatorial orientation of the OH group.

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* For Part 10, see Ref. 1.

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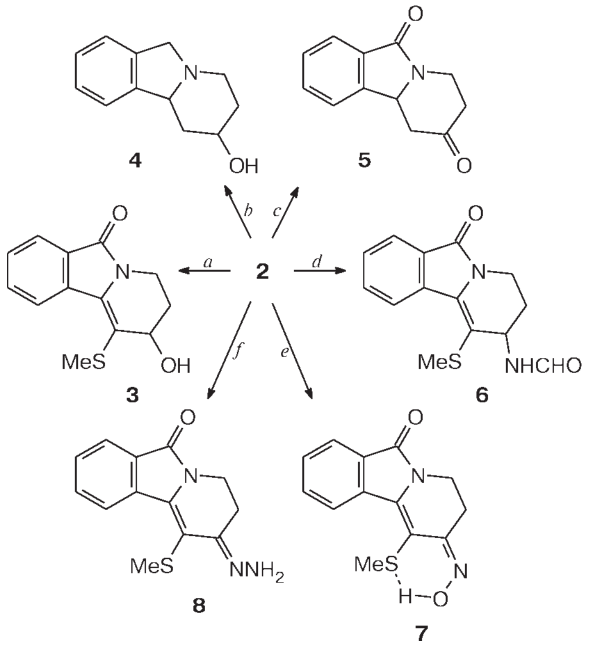
**Scheme 2**



**Reagents and conditions:** *a*. $NaBH_4$, EtOH, 0 °C; *b*. $LiAlH_4$, THF, ~20 °C; *c*. Zn, $NH_4Cl$, ~20 °C; *d*. $HCONH_2$, $HCO_2H$, 145 °C, 5 h; *e*. $NH_2OH \cdot HCl$, 90 °C; *f*. $NH_2NH_2 \cdot H_2O$, AcOH.

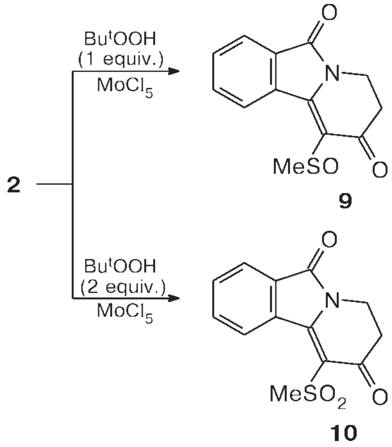
Desulfurization of indolizidinedione **2** with Raney nickel afforded a complex mixture of products. This reaction with the use of zinc dust in a saturated solution of ammonium chloride gave rise to reductive desulfurization product **5** in 60% yield. In the latter case, the double bond was also reduced (see Scheme 2, path *c*).

The reactions of indolizidinedione **2** with nitrogen nucleophiles proceeded through a mechanism typical of the keto group. Thus, the Leuckart reaction of compound **2** with formamide afforded formyl derivative **6** in 35% yield (see Scheme 2, path *d*). It should be noted that the addition of Raney nickel has no substantial effect on the reaction time and the yield of the product. The reactions of indolizidinedione **2** with hydroxylamine and hydrazine hydrate gave rise to oxime **7** and hydrazone **8** in 64% and 70% yields, respectively (see Scheme 2, paths *e* and *f*, respectively). Interestingly, there is an intramolecular hydrogen bond between the proton of the hydroxy group of oxime **7** and the S atom of the thiomethyl group, which is confirmed by a downfield shift of the signal for this protons to $\delta_H$ 12.01 and the shift of the absorption band of the OH group in the IR spectrum to ν 3200—3400 $cm^{-1}$.

The formation of the dioxolane derivative was not observed in the reaction of indolizidinedione **2** with ethylene glycol due, apparently, to steric hindrances associated with the presence of the thiomethyl substituent in the α position with respect to the keto group.

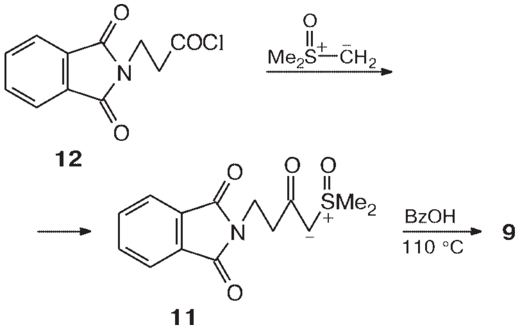
Oxidation of compound **2** with $Bu^tOOH$ in the presence of $MoCl_5$ afforded either sulfoxide **9** or sulfone **10** depending on the amount of the hydroperoxide used (Scheme 3). In the $^1H$ NMR spectra of compounds **9** and **10**, the signals for the protons of the methyl group bound to the S atom are shifted downfield compared to the analogous signals in the spectrum of the starting compound **2**.

**Scheme 3**



Sulfoxide **9** was prepared also by intramolecular cyclization of sulfoxonium ylide **11** (Scheme 4). Ylide **11** was obtained in 65% yield by acylation of Corey's ylide with *N*-phthaloyl-β-alanine acid chloride (**12**). Intramolecular cyclization, which proceeded on refluxing of ylide **11** in toluene in the presence of an equimolar amount of benzoic acid, produced sulfoxide **9** in 50% yield.

**Scheme 4**



## Experimental

The IR spectra were recorded on UR-20 and Specord M-80 instruments (in a thin layer or Nujol mulls). The $^1H$ and $^{13}C$ NMR spectra were measured on a Bruker AM-300 spectrometer (300 and 75 MHz, respectively) with $Me_4Si$ as the internal standard. The course of the reaction was monitored by TLC on Silufol UV-254 plates (Czech Republic); spots were visualized with UV light, iodine vapor or by spraying the plates with an anisaldehyde—$H_2SO_4$ mixture, which was prepared according to a known procedure,[3] followed by heating to 100—120 °C. The reaction products were isolated by column chromatography on silica gel. *tert*-Butyl hydroperoxide (5.0 *M* solution in *n*-decane; Aldrich, Cat. No. 41,666-5) was used without additional purification.

**1-Methylthio-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione (2)** was prepared according to a known procedure.[2]

**2-Hydroxy-1-methylthio-3,4-dihydropyrido[2,1-*a*]isoindol-6(2*H*)-one (3).** Sodium borohydride (0.6 g, 0.015 mol) was added portionwise with stirring to a solution of dione **2** (3 g, 0.012 mol) in EtOH (30 mL) at 0 °C. The reaction mixture was stirred for 40 min and warmed to ~20 °C. Then MeOH (40 mL) was added. After 15 min, the solvent was evaporated and then $H_2O$ (20 mL) and AcOEt (40 mL) were added. After stirring, the organic layer was separated and dried over $MgSO_4$. The solvent was evaporated. Compound **3** was obtained in a yield of 2.12 g (70%), m.p. 150—152 °C (from $Et_2O$). Found (%): C, 62.91; H, 5.11; N, 5.63; S, 11.40. $C_{13}H_{13}NO_2S$. Calculated (%): C, 63.13; H, 5.30; N, 5.66; S, 12.96. IR (Nujol mulls), $\nu/cm^{-1}$: 1608, 1656, 3264. $^1H$ NMR ($CDCl_3$), δ: 2.03—2.12 (m, 2 H, $CH_2$); 2.45 (s, 3 H, MeS); 3.68—4.10 (m, 2 H, $CH_2$); 4.60 (m, 1 H, CH); 7.79—8.32 (m, 4 H, Ar); 8.80 (s, 1 H, OH). $^{13}C$ NMR ($CDCl_3$), δ: 16.1, 30.0, 33.4, 64.7, 117.8, 123.0, 124.9, 129.2, 129.6, 131.9, 134.4, 136.9, 165.3.

**2-Hydroxy-1,2,3,4,6,10a-hexahydropyrido[2,1-*a*]isoindole (4).** Lithium aluminum hydride (0.4 g, 0.012 mol) was added to a solution of dione **2** (1 g, 0.004 mol) in anhydrous THF (20 mL) at ~20 °C under argon and the reaction mixture was refluxed with stirring for 5 h. Then $Et_2O$ (15 mL) and a 10% NaOH solution (2 mL) were added. The precipitate that formed was filtered off, the solvent was evaporated, and the residue was chromatographed (successive elution with AcOEt and EtOH). The alcohol fraction was concentrated. Compound **4** was obtained in a yield of 0.27 g (35%), m.p. 148—151 °C (from acetone). Found (%): C, 76.00; H, 7.83; N, 7.35. $C_{12}H_{15}NO$. Calculated (%): C, 76.16; H, 7.99; N, 7.40. IR, $\nu/cm^{-1}$: 3160. $^1H$ NMR (acetone-$d_6$), δ: 1.36 (dt, 1 H, $C(1)H_{ax}$, $J$ = 12.3 Hz, $J$ = 11.4 Hz); 1.58 (m, 1 H, $C(3)H_{ax}$); 1.88 (m, 1 H, $C(3)H_{eq}$); 2.42 (dd, 1 H, $C(1)H_{eq}$, $J$ = 12.3 Hz, $J$ = 4.7 Hz); 2.57 (m, 1 H, $C(4)H_{ax}$); 3.08 (m, 1 H, $C(4)H_{eq}$); 3.34 (dd, 1 H, C(10a)H, $J$ = 11.4 Hz, $J$ = 3.1 Hz); 3.48 (dd, 1 H, $C(6)H_a$, $J$ = 12.0 Hz, $J$ = 3.1 Hz); 3.71 (td, 1 H, $C(2)H_{ax}$, $J$ = 11.4 Hz, $J$ = 4.7 Hz); 4.02 (d, 1 H, $C(6)H_b$, $J$ = 12.0 Hz); 3.50 (br.s, 1 H, OH); 7.10—7.23 (m, 4 H, Ar). $^{13}C$ NMR (acetone-$d_6$), δ: 36.0, 39.4, 49.5, 57.5, 66.7, 70.0, 121.4, 123.4, 127.6, 142.4, 145.6.

**1,3,4,10a-Tetrahydropyrido[2,1-*a*]isoindole-2,6-dione (5).** A suspension of zinc dust (7 g) in a saturated solution of $NH_4Cl$ (15 mL) was added to a solution of dione **2** (0.25 g, 1 mmol) in THF (20 mL) and the reaction mixture was stirred for 1.5 h. Then $H_2O$ (20 mL) was added and the mixture was extracted with AcOEt. The extract was washed with a 5% $Na_2CO_3$ solution and dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed through a short layer of $Al_2O_3$. Compound **5** was obtained in a yield of 0.12 g (60%). Found (%): C, 71.50; H, 4.90; N, 6.56. $C_{12}H_{11}NO_2$. Calculated (%): C, 71.63; H, 5.51; N, 6.96. IR (Nujol mulls), $\nu/cm^{-1}$: 1664, 1792. $^1H$ NMR ($CDCl_3$), δ: 2.23, 2.93, and 3.45 (all m, 2 H each, $CH_2$); 4.68 (m, 1 H, CH); 7.35—8.10 (m, 4 H, Ar). $^{13}C$ NMR ($CDCl_3$), δ: 37.3, 39.6, 46.2, 57.7, 121.7, 124.2, 128.8, 131.5, 131.9, 144.2, 166.1, 205.7.

***N*-(1-Methylthio-6-oxo-2,3,4,6-tetrahydropyrido[2,1-*a*]isoindol-2-yl)formamide (6).** A mixture of $HCO_2H$ (0.092 g) and $HCONH_2$ (5 mL) was heated to 130 °C and then dione **2** (0.1 g, 0.04 mmol) was added portionwise. The reaction mixture was heated to 145 °C and the temperature was kept constant for 5 h. Then the reaction mixture was cooled, $H_2O$ (10 mL) was added, the mixture was extracted with $CHCl_3$, the extract was dried over molten NaOH, and the solvent was distilled off. The product was isolated by column chromatography (9 : 1 $CHCl_3$—$Me_2CO$ mixture as the eluent). Compound **6** was obtained in a yield of 0.038 g (35%), m.p. 187—189 °C. Found (%): C, 60.90; H, 5.10; N, 9.50; S, 11.20. $C_{14}H_{14}N_2O_2S$. Calculated (%): C, 60.29; H, 5.14; N, 10.20; S, 11.60. IR (Nujol mulls), $\nu/cm^{-1}$: 1715, 1776. $^1H$ NMR (DMSO-$d_6$), δ: 2.15 (m, 2 H, $CH_2$); 2.38 (s, 3 H, SMe); 3.50 (t, 2 H, $CH_2$, $J$ = 13.4 Hz); 4.20 (m, 1 H, CH); 5.15 (d, 1 H, NH, $J$ = 8.1 Hz); 7.70—8.10 (m, 4 H, Ar); 8.25 (s, 1 H, CHO). $^{13}C$ NMR (DMSO-$d_6$), δ: 15.0, 28.1, 33.7, 42.5, 116.3, 122.7, 124.7, 129.4, 129.7, 132.3, 133.3, 134.1, 160.4, 163.8.

**2-Hydroxyimino-1-methylthio-3,4-dihydropyrido[2,1-*a*]isoindole-6(2*H*)-one (7).** A solution of dione **2** (0.1 g, 0.4 mmol) in MeOH (5 mL) was added dropwise with stirring to a solution of $NH_2OH \cdot HCl$ (0.083 g, 1.2 mmol) in Py (5 mL). The reaction mixture was heated to 90 °C and stirred at this temperature for 1.5 h. Then the solvent was distilled off. The crystalline compound that formed was washed with water, recrystallized from aqueous EtOH, and dried *in vacuo*. Compound **7** was obtained as pale-yellow crystals in a yield of 0.066 g (64%), m.p. 196—198 °C. Found (%): C, 60.00; H, 4.50; N, 10.10; S, 12.20. $C_{13}H_{12}N_2O_2S$. Calculated (%): C, 59.98; H, 4.56; N, 10.76; S, 12.32. IR (Nujol mulls), $\nu/cm^{-1}$: 1670, 1775, 3400. $^1H$ NMR (DMSO-$d_6$), δ: 2.38 (s, 3 H, SMe); 2.90 and 3.78 (both t, 2 H each, $CH_2$, $J$ = 7.7 Hz); 7.55—8.25 (m, 4 H, Ar); 12.01 (s, 1 H, CHO). $^{13}C$ NMR (DMSO-$d_6$), δ: 21.9, 25.7, 40.6, 116.9, 127.9, 130.3, 134.6, 135.2, 136.6, 137.4, 143.6, 154.9, 169.3.

**2-Hydrazono-1-methylthio-3,4-dihydropyrido[2,1-*a*]isoindole-6(2*H*)-one (8).** Acetic acid (0.1 g, 1.7 mmol) was added to a hot solution of dione **2** (0.5 g, 2 mmol) and $N_2H_4 \cdot H_2O$ (0.4 g, 6 mmol) in EtOH (15 mL). The reaction mixture was refluxed for 1 h, cooled to ~20 °C, and kept for 1 h. The needle-like yellow crystals that precipitated were filtered off and dried. Compound **8** was obtained in a yield of 0.44 g (86%), m.p. 205—207 °C (from EtOH). Found (%): C, 59.90; H, 4.56; N, 16.14; S, 12.15. $C_{13}H_{13}N_3OS$. Calculated (%): C, 60.21; H, 5.05; N, 16.20; S, 12.36. IR (Nujol mulls), $\nu/cm^{-1}$: 1690, 3410. $^1H$ NMR (DMSO-$d_6$), δ: 2.47 (s, 3 H, Me); 2.87 and 3.85 (both t, 2 H each, $CH_2$, $J$ = 6.7 Hz); 7.05 (s, 2 H, $NH_2$); 7.55—8.88 (m, 4 H, Ar). $^{13}C$ NMR (DMSO-$d_6$), δ: 18.1, 20.7, 35.8, 116.7, 122.7, 125.4, 129.1, 129.2, 132.0, 134.7, 134.8, 137.9, 164.0.

**1-Methylsulfinyl-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione (9).** *tert*-Butyl hydroperoxide (0.9 g, 0.01 mmol) was added to a solution of dione **2** (2.47 g, 0.01 mol) and $MoCl_5$ (0.01 g, 0.36 mmol) in dioxane (50 mL). The reaction mixture was refluxed for 0.5 h and then cooled. The solvent was evaporated and the residue was chromatographed through a short layer of $Al_2O_3$. Compound **9** was obtained in a yield of 1.97 g

(75%), m.p. 210—212 °C. Found (%): C, 59.13; H, 4.10; N, 5.28; S, 10.96. $C_{13}H_{11}NO_3S$. Calculated (%): C, 59.76; H, 4.24; N, 5.36; S, 12.27. IR (Nujol mulls), $\nu$/cm$^{-1}$: 1572, 1664, 1724. $^1$H NMR ($CDCl_3$), $\delta$: 2.85 (t, 2 H, $CH_2$, $J$ = 7.2 Hz); 3.22 (s, 3 H, Me); 3.82—4.44 (m, 2 H, $CH_2$); 7.62—8.63 (m, 4 H, Ar). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 36.1, 36.7, 38.7, 118.8, 124.5, 129.5, 129.7, 133.0, 133.2, 133.7, 159.6, 189.3.

**1-Methylsulfonyl-3,4-dihydropyrido[2,1-*a*]isoindole-2,6-dione (10)** was prepared from dione **2** analogously to sulfoxide **9** by adding 2 equiv. of Bu$^t$OOH. Compound **10** was obtained in a yield of 1.98 g (71%), m.p. 181—185 °C. Found (%): C, 56.98; H, 3.97; N, 4.57; S, 10.24. $C_{13}H_{11}NO_4S$. Calculated (%): C, 56.31; H, 4.00; N, 5.05; S, 11.56. IR (Nujol mulls), $\nu$/cm$^{-1}$: 1536, 1656, 1672, 1736. $^1$H NMR (DMSO-$d_6$), $\delta$: 2.85 (t, 2 H, $CH_2$, $J$ = 7.1 Hz); 3.41 (s, 3 H, Me); 4.12 (t, 2 H, $CH_2$, $J$ = 7.1 Hz); 7.70—8.50 (m, 4 H, Ar). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 35.3, 35.6, 42.0, 118.3, 123.7, 129.3, 132.0, 133.4, 133.6, 134.2, 154.8, 165.1, 189.8.

**1-Dimethyloxosulfuranylidene-4-phthalimidobutan-2-one (11).** Acid chloride **12** (1.18 g, 0.005 mol) was added dropwise with stirring to a solution of dimethyloxosulfonium methylide[**4**] (1.04 g, 0.012 mol) in THF (30 mL) at ~20 °C (compoud **12** was prepared according to a procedure reported previously[**5**]). The reaction mixture was stirred for 2 h and the precipitate that formed was filtered off. After evaporation of the mother liquor, ylide **11** was obtained in a yield of 1.0 g (80%). Found (%): C, 57.13; H, 4.93; N, 4.70; S, 9.75. $C_{14}H_{15}NO_4S$. Calculated (%): C, 57.32; H, 5.15; N, 4.77; S, 10.93. IR (Nujol mulls), $\nu$/cm$^{-1}$: 1545, 1620, 1710, 1770. $^1$H NMR ($CDCl_3$), $\delta$: 2.33 (t, 2 H, $CH_2$, $J$ = 7 Hz); 3.18 (s, 3 H, Me); 3.76 (t, 2 H, $CH_2$, $J$ = 7 Hz); 4.03 (s, 1 H, CH); 7.45—7.50 (m, 4 H, Ar). $^{13}$C NMR ($CDCl_3$), $\delta$: 35.5, 39.0, 42.2, 70.6, 123.2, 132.2, 134.0, 168.2, 186.8.

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