An Unexpected Preparation of 4-Oxo-2*H*-1,3-benzothiazines

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Received August 27, 1983

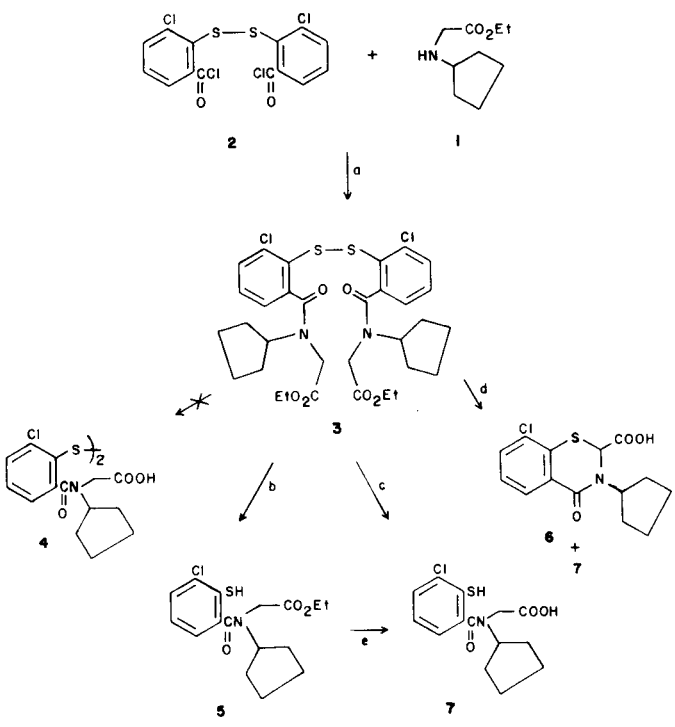
Treatment of compound *N,N*-(dithiobis(3-chloro-2,1-phenylene)dicarbonylbis(*N*-cyclopentylglycine)diethyl ester (**3**) with methanolic sodium hydroxide does not produce the expected hydrolysis product *N,N*-(dithiobis-(3-chloro-2,1-phenylene)dicarbonylbis(*N*-cylcopentylglycine) (**4**) but yields a mixture of compounds 8-chloro-3-cyclopentyl-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine-2-carboxylic acid (**6**) and *N*-(3-chloro-2-mercaptobenzoyl)-*N*-cyclopentylglycine (**7**). This unexpected observation has the potential of a new heterocyclic synthesis method for the 4-oxo-2*H*-1,3-benzothiazine class of compounds.

J. Heterocyclic Chem., **20**, 1755 (1983).

During an investigation of the preparation of angiotensin converting enzyme (ACE) inhibitors [1], we observed an unusual reaction which has the potential for a new general heterocyclic synthesis.

Compound **3**, prepared as shown [2], was reduced with sodium borohydride in methanol (Route b) to give the expected **5** in high yield. This was converted to **7** on hydrolysis (Scheme I).

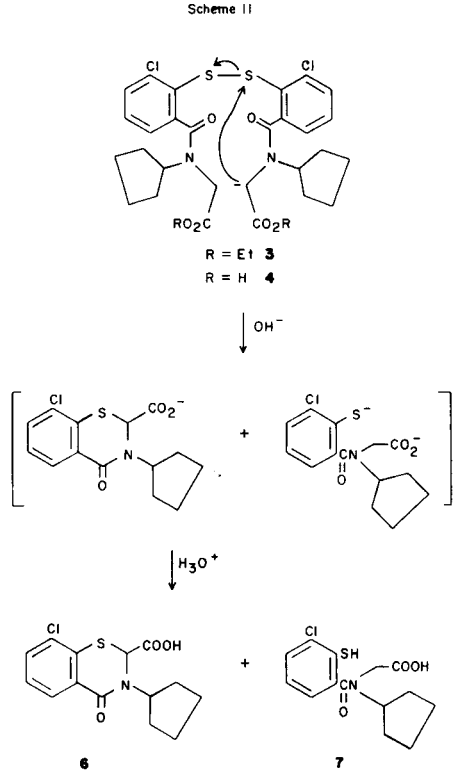
Scheme I [a]



[a] Toluene, Et_3N, 23°C, 4 1/2 h, (52%); [b] MeOH, $NaBH_4$, rt, 5 1/2 h, (90%); [c] MeOH/H_2O (2/1), $Na_2S_2O_4$, NaOH, rt, 16 h, (72%); [d] MeOH/H_2O (3/1), NaOH (3 equiv), rt, 17 h, (6 (15%) and 7 (17%)).

When compound **3** was first treated with methanolic sodium hydroxide two products were obtained. One of these was identical to **7**, the other was the unexpected cyclized product.

Scheme II



The structure of **6** was proven as follows.

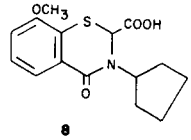
Compound **6** gave a negative test with nitroprusside spray reagent indicating the lack of a mercapto group. The ir spectrum displayed bands at 1740, 1615 and 1585 cm^{-1} indicating an intact carboxylic acid and amide functionalities. The ^1H nmr spectrum showed a well defined aromatic ABX pattern, a one proton resonance at 12.80

ppm, which exchanged with deuterium oxide and two unique one proton resonances at 4.93 (multiplet) and 5.37 (singlet) ppm. The mass spectrum indicated m/e 313 (M^+ + 2, Cl isotope), 311 (M^+), 268 (M^+ + 2, $-CO_2H$, Cl isotope), and 266 (M^+, $-CO_2H$); along with the elemental analysis this provided a molecular formula of $C_{14}H_{14}NO_3ClS$.

Mechanistically, compound **6** can be envisioned as arising from an internal anion alkylation which produces **7** as a leaving group group (Scheme II).

We are unaware of this type of a reaction having been previously reported in the literature and believe this reaction constitutes an approach to the synthesis [3] of this interesting class of heterocyclic compounds.

A similar reaction was observed with the methoxy analog **8** [4].



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EXPERIMENTAL

Nuclear Magnetic Resonance (^1H nmr) spectra were recorded on a Varian EM 360L spectrometer and chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard. Infrared (ir) spectra, reported in reciprocal centimeters, were recorded as potassium bromide pellets on a Perkin Elmer Model 299B infrared spectrophotometer. Mass spectra (ms) were recorded on a Varian MAT 112 spectrometer with an SS-100C data system in the direct probe mode. Mass spectral data and elemental analyses were obtained by the Revlon Health Care Group, Analytical Research Department. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Analytical thin layer chromatography (tlc) was carried out by using Merck silica gel 60 F-254 (5 × 10 cm) plates.

N,N-Dithiobis(3-chloro-2,1-phenylene)dicarbonylbis(*N*-cyclopentylglycine)diethyl Ester (**3**).

To a solution of ethyl *N*-(cyclopentyl)glycinate **1** (147.5 g, 866.5 mmoles) in 2.0 ℓ of toluene containing triethylamine (87.7 g, 866.5 moles) cooled to 0-5° was added 2,2'-dithiobis(3-chlorobenzoyl)chloride (**2**) (170.0 g, 824.9 mmoles) portionwise. The reaction was exothermic, and the protionwise addition was controlled to maintain the internal temperature below 23°. After 4 ½ hours, the reaction mixture was partitioned with 500 ml of 20% aqueous hydrochloric acid, 500 ml of saturated sodium bicarbonate and 500 ml of water. The solvent was evaporated *in vacuo* and the residue triturated with 250 ml of ether to yield compound **3**, 145.5 g (52%); mp 133-137°; ir (potassium bromide): 1740, 1630, 790, 745, 720 cm^{-1}; ^1H nmr (deuteriochloroform): 7.30 (6 H, br m), 4.10 (10 H, br m), 1.53 (22 H, br m) ppm; ms: (EI) m/e 340 /(M^+/2).

Anal. Calcd. for $C_{32}H_{38}Cl_2N_2O_6S_2$: C, 56.38; H, 5.45; N, 4.11. Found: C, 56.73; H, 5.45; N, 3.80.

Ethyl *N*-(3-Chloro-2-mercaptobenzoyl)-*N*-cyclopentylglycinate (**5**).

Compound **3** (10.0 g,14.7 mmoles) was suspended in methanol (100 ml) and sodium borohydride (1.5 g, 40.4 mmoles) was added in three equal portions over a 3 hour interval. After 2 ½ hours additional reaction time excess sodium borohydride was decomposed by the addition of 20 ml of glacial acetic acid/water (1/10) and the solution concentrated *in vacuo* to yield compound **5**, 8.9 g (90%). An analytical sample was crystallized from ether/2,2,4-trimethylpentane as white needles; mp 70-73°; ir (potassium bromide): 2550, 1755, 1645 cm^{-1}; ^1H nmr (deuteriochloroform): 7.15 (3 H, m), 4.70 (1 H, s, exchanges with deuterium oxide), 4.23 (2 H, q), 3.95 (3 H, m), 1.62 (8 H, b), 1.33 (3 H, t) ppm; ms: (EI) m/e 341 (M^+).

Anal. Calcd. for $C_{16}H_{20}ClNO_3S$: C, 56.31; H, 5.89; N, 4.09. Found: C, 56.43; H, 6.00; N, 3.78.

N-(3-Chloro-2-mercaptobenzoyl)-*N*-cyclopentylglycine (**7**).

Compound **3** (1.6 g, 2.3 mmoles) was dissolved in a solution of sodium dithionite (2.5 g, 14.4 mmoles) and sodium hydroxide (2.5 g, 62.5 mmoles) in 75 ml of methanol/water (2/1). After 16 hours at room temperature the solution was concentrated *in vacuo* and the residue partitioned with ethyl acetate (100 ml) and 2*N* aqueous hydrochloric acid (200 ml) and the ethyl acetate removed to yield **7**, 1.2 g (72%). An analytical sample was crystallized from ethyl acetate/2,2,4-trimethylpentane as a white solid, mp 160-163.5°; ir (potassium bromide): 3450, 2515, 1760, 1590 cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): 7.20 (5 H, br m, 2 H exchanges with deuterium oxide), 3.85 (3 H, br), 1.58 (8 H, b) ppm; ms: (EI) m/e 313 (M^+).

Anal. Calcd. for $C_{14}H_{16}ClNO_3S$: C, 53.58; H, 51.4; N, 4.46. Found: C, 53.63; H, 5.11; N, 4.26.

N-(3-Chloro-2-mercaptobenzoyl)-*N*-cyclopentylglycine (**7**) and 8-Chloro-3-cyclopentyl-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine-2-carboxylic Acid (**6**).

Compound **3** (52.5 g, 77.0 mmoles) was dissolved in 200 ml of methanol/water (3/1) and sodium hydroxide pellets (9.3 g, 231.0 mmoles) were added in two equal portions over a 1 hour interval. After 16 hours at room temprature the solvent was removed *in vacuo* and the residue partitioned with methylene chloride (100 ml) and water (200 ml). The basic aqueous layer was acidified to *p*H 2.0 with concentrated hydrochloric acid and extracted with ethyl acetate (500 ml). Removal of ethyl acetate yielded 34.1 g of a white foam which showed two spots by tlc (chloroform/methanol/acetic acid, 85/15/5): compound **7** R_f 0.47 and compound **6** R_f 0.40 in a 1/1 ratio. The crude mixture was fractionally recrystallized from ethyl acetate/hexane to yield 7.23 g (15%) of compound **6** as a single component by tlc. Concentration and crystallization of the mother liquor yielded 8.3 g (17%) of compound **7** as a single component by tlc, mp 160-163°. The ^1H nmr spectrum of this sample was identical to compound **7** obtained previously (*vide supra*). An analytical sample of compound **6** was obtained by recrystallization from glacial acetic acid, mp 260-262°; ir (potassium bromide): 2540, 1740, 1615, 1585, 1560, 750, 675 cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): 12.80 (1 H, b, exchanges with deuterium oxide), 7.92 (1 H, dd), 7.40 (1 H, dd), 7.20 (1 H, q), 5.37 (1 H, s), 4.93 (1 H, m), 1.67 (8 H, b) ppm; ms: (EI) m/e 313 (M^+ + 2, Cl isotope), 311 (M^+), 268, 266, 200, 199, 198.

Anal. Calcd. for $C_{14}H_{14}ClNO_3S$: C, 53.93; H, 4.53; N, 4.49. Found: C, 53.72; H, 4.43; N, 4.32.

Acknowledgment.

We thank Dr. I. Basco, Dr. B. Loev and Dr. L. Reilly for helpful discussions concerning the preparation of this manuscript and Ms. Susan Ciamarra for the typing.

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[4] Compound **8**, 8-methoxy-3-cyclopentyl-3,4-dihydro-4-oxo-2*H*-1,3-benzothiazine-2-carboxylic acid, mp 277° was prepared by procedures similar to those described for compound **6** and was characterized by ir, nmr, ms (CI and EI) and elemental analysis.