

Synthesis of 2*H*-1,4-Thiazin-3(4*H*)-one 1-Oxide and 2*H*-1,4-Thiazin-3(4*H*)-one 1,1-Dioxide, Structural Analogs of Uracil

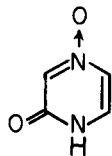
M. Bobek

Grace Cancer Drug Center, Roswell Park Memorial Institute,
666 Elm Street, Buffalo, NY 14263
Received August 12, 1981

The synthesis of 1,4-thiazine 1-oxide and 1,1-dioxide analogs of the antibiotic emimycin is described. Reaction of methylthioglycolate with 1-bromo-2,2-diethoxyethane gave methyl (2,2-diethoxyethylthio)acetate (**2**). Treatment of **2** with methanolic ammonia followed by cyclization furnished 2*H*-1,4-thiazin-3(4*H*)-one (**5**). Oxidation of **5** with *m*-chloroperoxybenzoic acid converted it to 2*H*-1,4-thiazin-3(4*H*)-one 1-oxide (**6**). Oxidation of **2** with potassium permanganate, followed by treatment with methanolic ammonia, and cyclization gave 2*H*-1,4-thiazin-3(4*H*)-one 1,1-dioxide.

J. Heterocyclic Chem., **19**, 131 (1982).

The replacement of the pyrimidine ring of the natural pyrimidines with other heterocycles, such as 1,3,5-triazine (**1**) pyridine (**2**), and 1,2,4-triazine (**3**), has resulted in a number of biologically active analogs. On such modification, the substitution of a pyrazine for the pyrimidine ring of uracil, occurs in the antibiotic emimycin (**4,5**) (**1**). Because of the antimetabolite properties (**6,7**) of emimycin, it was of interest to prepare other similarly modified analogs of uracil. This communication reports the synthesis of 1,4-thiazine derivatives **6** and **9** in which the 4 carbonyl is replaced by the bioisosteric (**8**) SO and/or SO₂ groups.



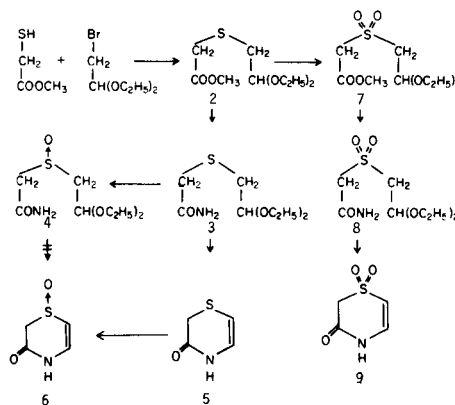
1

Chemistry.

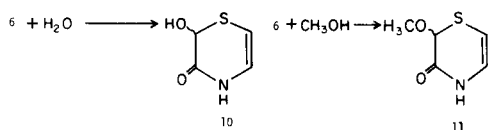
Alkylation of methyl thioglycolate with 1-bromo-2,2-diethoxyethane in the presence of sodium methoxide gave methyl (2,2-diethoxyethylthio)acetate (**2**, Scheme I). Treatment of **2** with methanolic ammonia gave intermediate (2,2-diethoxyethylthio)acetamide (**3**) which was oxidized by *m*-chloroperoxybenzoic acid to give the corresponding sulfoxide **4**. While acid-catalyzed cyclization of **4** was unsuccessful and produced only intractable mixtures, similar cyclization of the sulfide **3** gave 2*H*-1,4-thiazin-3(4*H*)-one (**5**) in good yield. Oxidation of **5** with *m*-chloroperoxybenzoic acid furnished 2*H*-1,4-thiazin-3(4*H*)-one 1-oxide (**6**) in high yield. The sulfoxide derivatives **6** proved to be unstable, decomposing slowly when exposed to air. However, compound **6** could be kept without decomposition under an inert atmosphere (nitrogen). Since it appeared that the atmospheric moisture was the cause for the decomposition of **6**, it was of interest to study the product of the reaction of **6** and water. Compound **6**, when

dissolved in cold water (0-2°), underwent a Pummerer-type reaction to give 2*H*-2-hydroxy-1,4-thiazin-3(4*H*)-one (**10**, Scheme II). Similarly, reaction of **6** with methanol produced 2*H*-2-methoxy-1,4-thiazin-3(4*H*)-one (**11**). Although the facility of the reaction of **6** with water and/or methanol is surprising, the reaction appears to be consistent with the Pummerer rearrangement of sulfoxides under the influence of acidic catalysts (**9-12**), water and methanol being both reactants and catalysts. Thus, the reaction of **6** with methanol (*p*K_a ~ 18) was much slower than the similar reaction of **6** with water (*p*K_a ~ 15.8). Attempts to oxidize the thiazine derivatives **5** and/or **6** to the corresponding thiazine dioxide **9**, using *m*-chloroperoxybenzoic acid or trifluoroperoxyacetic acid under varied experimental conditions, led to complex mixtures. Methyl (2,2-diethoxyethylthio)acetate (**2**) was therefore oxidized with potassium permanganate (**13**) to give a mixture of methyl (2,2-diethoxyethylsulfonyl)acetate (**7**) and some unchanged **2**. The mixture was treated with methanolic ammonia to give a mixture of the corresponding amides **3** and **8**, followed by acid-catalyzed cyclization to furnish **5** and 2*H*-1,4-thiazin-3(4*H*)-one 1,1-dioxide (**9**).

Scheme I



Scheme 11



EXPERIMENTAL

PMR spectra were recorded on a Varian XL-100 spectrometer with tetramethyl-silane as an internal reference. Mass spectra were obtained on a CEC 21-491 double focusing mass spectrometer using an ionization voltage 70 eV. All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The uv spectra were determined on a Cary 14 spectrophotometer. Evaporations were carried out under reduced pressure on a rotary evaporator.

Methyl (2,2-Diethoxyethylthio)acetate (2)

To a cold (0-5°), stirred solution of sodium methoxide (prepared from 24 g of sodium) in methanol (400 ml) was added, dropwise and under a stream of nitrogen, methyl mercaptoacetate (106 g, 1 mole), followed by bromoacetaldehyde diethylacetal (197 g, 1 mole). The reaction mixture which spontaneously warmed to reflux temperature was heated for 1 hour and cooled to room temperature. Solid carbon dioxide (20 g) was added, the mixture was filtered, and the filtered salts were washed with methylene chloride (200 ml). The combined filtrates were evaporated to an oil which was taken up in methylene chloride (600 ml). This solution was washed with water (2 × 200 ml), dried (sodium sulfate) and evaporated. The oily residue was distilled at a reduced pressure to give 172.8 g (77.7%) of **2**, bp (0.01 mm Hg) 85-86°, bp (9 mm Hg) 129-130°; ms: M⁺ 222.

2H-1,4-Thiazin-3(4H)-one (5)

A solution of **2** (111.2 g, 0.5 mole) in methanol (250 ml) was saturated with ammonia at room temperature, kept for 16 hours, and evaporated to a syrup. The syrup was dissolved in toluene (200 ml), *p*-toluenesulfonic acid (100 mg) was added, and the solution was heated at reflux temperature for 1 hour. Triethylamine (1 ml) was added to the cooled solution which was then evaporated. The residue was dissolved in toluene-acetone (9:1, 800 ml). Silica gel was added to this solution with stirring, the mixture was filtered, the solids were washed with toluene-acetone (9:1, 100 ml), and the combined-filtrates were evaporated. The residue was dissolved in toluene-ether (5:2, 100 ml) and crystallized overnight. The product was filtered and washed with toluene-ether, yield 25.5 g. Evaporation of the filtrate and purification of the residue by silica-gel chromatography (benzene-ethyl acetate, 4:1) and crystallization gave 17 g of **5**. The total yield of **5** was 42.5 g (73.8%), mp 76-77°; uv (ethanol): max 299 nm; ms: m/e 115; nmr (acetone-d₆): δ 8.86 (br. s, 1, H-4), 6.26 (q, 1, J = 7.5, 3 Hz, H-5), 5.56 (q, 1, J = 1 and 7.5 Hz, H-6), 3.21 (d, 2, H = 1, H-2).

Anal. Calcd. for C₄H₅NOS: C, 41.75; H, 4.37; N, 12.16; S, 27.84. Found: C, 41.85; H, 4.40; N, 12.08; S, 27.52.

(2,2-Diethoxyethylsulfanyl)acetamide (4)

A solution of **2** (22.2 g, 0.1 mole) in methanol (100 ml) was saturated with ammonia at room temperature, kept for 16 hours, and evaporated. The oily residue was dissolved in methylene chloride (200 ml) and the solution was cooled to ~0°. *m*-Chloroperoxybenzoic acid (85%, 22 g, 0.11 mole) was added in small parts with stirring over a 30 minutes period and the mixture was stirred at 0° for 1 hour. A saturated solution of sodium hydrogen carbonate (250 ml) was added, the mixture stirred for 1 hour and evaporated to dryness. The residue was extracted with methylene chloride (3 × 200 ml), filtered, the filtrate was evaporated, and the residue was crystallized from benzene to give 17.1 g (76.6%) of **4**, mp 93-94°.

Anal. Calcd. for C₈H₁₇NO₄S: C, 43.03; H, 7.67; N, 6.27; S, 14.36. Found: C, 43.18; H, 7.80; N, 6.08; S, 14.16.

2H-1,4-Thiazin-3(4H)-one 1-Oxide (6)

m-Chloroperoxybenzoic acid (85%, 5.7 g) was added under nitrogen, and with stirring to a cold (-40°) solution of **5** (3.46 g, 0.03 mole) in 1,2-dichloroethane (120 ml)-ethyl acetate (40 ml). The mixture was stirred at -40° for 1 hour and the precipitated product was filtered under nitrogen, washed with dry ether (200 ml), 1% pyridine in ether (50 ml) and dried in a stream of nitrogen, yield 3.57 g (90.5%) of **6**. The uv spectra of **6** when taken in water or methanol showed an absorption peak at 266 nm which shifted to 282 nm during 1 hour in water and to 281 nm during 4 hour in methanol; nmr (dimethyl sulfoxide-d₆): δ 8.48 (br. s, 1, H-4) 7.05 (q, 1, J = 8 and 6 Hz, H-5), 6.23 (d, 1, J = 8 Hz, H-6) 3.87 (s, 2, H-2).

Anal. Calcd. for C₄H₅NO₂S: C, 36.63; H, 3.84; N, 10.68. Found: C, 36.37; H, 3.97; N, 10.33.

2H-1,4-Thiazine-3(4H)-one 1,1-Dioxide (9)

A solution of **2** (22.2 g, 0.1 mole) in methylene chloride (200 ml) was added to solution of magnesium sulfate (30 g) in water (300 ml). Potassium permanganate (31.6 g, 0.6 mole) was added to the stirred mixture during 1 hour and the mixture was stirred at room temperature overnight. It was then filtered and the precipitate was washed with methylene chloride (100 ml). The water phase was separated and washed with methylene chloride (2 × 100 ml). The combined methylene chloride solution was dried (sodium sulfate) and evaporated. The oily residue was dissolved in methanol (200 ml) and the solution saturated with ammonia at room temperature. The mixture was kept at room temperature for 8 hours, evaporated, and the oily residue dissolved in toluene-methanol (5:1, 400 ml). *p*-Toluene sulfonic acid (1 g) and water (10 ml) were added and the mixture was heated at reflux temperature for 2 hours. It was then evaporated and the residue separated by silica-gel chromatography in toluene-acetone (7:1 and 4:1, V/V) to give 2.2 g (19.1%) of **5** and 8.6 g (58.5%) of **9**, mp 154-155°; nmr (acetone-d₆): δ 9.56 (br. s, NH), 7.17 (d, 1, J = 8.8 Hz, H-5), 6.30 (q, 1, J = 1.3 and 8.8 Hz, H-6), 4.33 (d, 2, J = 1.3 Hz, H-2).

Anal. Calcd. for C₄H₅NO₃S: C, 32.65; H, 3.42; N, 9.52; S, 21.78. Found: C, 32.78; H, 3.56; N, 9.70; S, 21.60.

2H-2-Hydroxy-1,4-thiazin-3(4H)-one (10)

Compound **6** (2.52 g, 0.02 mole) was dissolved in cold water (50 ml, 0°) and the solution kept at 0° for 3 hours. Tlc of the mixture (benzene-acetone, 1:1) showed a single uv absorbing spot. The mixture was evaporated and the syrupy residue purified on a silica gel column in benzene-acetone (1:1, V/V), to give 1.1 g (41%) of **10**, mp 131-132°; uv (ethanol): max 282 nm; ms: m/e 131; nmr (dimethyl sulfoxide-d₆-deuteriumoxide): δ 6.52 (d, 1, J = 7.3, H-5), 5.67 (q, 1, J = 7.3 and 2 Hz, H-6), 5.16 (d, 1, J-2, H-2); (dimethyl sulfoxide-d₆): δ 8.48 (br. s, 1, H-4), 6.68 (d, 1, J = 6 Hz, OH) 6.43 (1, q, J = 5 and 7.5 Hz, H-5), 5.6 (q, 1, J = 7.5 and 2 Hz, H-6), 5.09 (q, 1, H-2).

Anal. Calcd. for C₄H₅NO₂S: C, 36.63; H, 3.84; N, 10.68. Found: C, 36.51; H, 3.98; N, 10.29.

2H-2-Methoxy-1,4-thiazin-3(4H)-one (11)

Compound **6** (2.62 g, 0.02 mole) was dissolved under nitrogen in cold (5°) methanol. The solution was kept at 4° for two days, evaporated, and the residue was purified by silica gel chromatography in benzene-acetone (9:1, V/V) to give 1.35 g (46.5%) of oily **11** which was crystallized from cyclohexane-ether (3:1), mp 60-61°; uv (ethanol): max 281 nm; nmr (deuteriochloroform): δ 8.00 (br. s, 1, H-4), 6.47 (1, q, H-5), 5.48 (q, 1, H-6) 4.86 (d, 1, H-2), 3.44 (s, 3 CH₃); ms: m/e 145.

Anal. Calcd. for C₅H₇NO₂S: C, 41.36; H, 4.85; N, 9.65. Found: C, 41.20; H, 5.02; N, 9.57.

Acknowledgement.

This investigation was supported in part by Grant CA13308 from the National Cancer Institute, USPHS.

REFERENCES AND NOTES

- (1) F. Sorm, A. Piskala, A. Cihak, and J. Vesely, *Experientia*, **20**, 202 (1964).
- (2) M. J. Robins, B. L. Curie, R. K. Robins and A. Bloch, *Proc. Am. Assoc. Cancer Res.*, **10**, 73 (1969).
- (3) J. J. Jaffe, R. E. Handschumacher and A. D. Welch, *Yale J. Biol. Med.*, **30**, 168 (1957).
- (4) M. Terao, K. Karasawa, N. Tanaka, H. Yonehara and H. Umezawa, *J. Antibiot.*, Ser. A., **13**, 401 (1960).
- (5) M. Terao, *ibid.*, Ser. A., **16**, 182 (1963).
- (6) J. R. De Zeeuw and E. J. Tyman, *ibid.*, Ser. A., **22**, 386 (1969).
- (7) M. Bobek and A. Bloch, *J. Med. Chem.* **15**, 164 (1972).
- (8) A. Burger, "Medicinal Chemistry", Part I, 3rd Ed, John Wiley and Sons, New York, N.Y., 1970, p 72.
- (9) R. Pummerer, *Ber.*, **42**, 2282 (1909).
- (10) L. Horner and P. Kaiser, *Ann. Chem.*, **626**, 19 (1959).
- (11) S. Oea, T. Kitao, S. Kawamura and Y. Kitaoka, *Tetrahedron*, **19**, 817 (1963).
- (12) F. Eiden and F. Meinel, *Arch. Pharm. (Weinheim)*, **312**, 302 (1979).
- (13) G. W. Gokel, H. M. Gerdes and D. M. Dishong, *J. Org. Chem.* **45**, 3634 (1980).