Thiazine Derivatives. III. The Synthesis of Some 2-Substituted 5,6-Dihydro-1,3(4H)-thiazines and Tetrahydro-1,3-thiazines Related to Cephams[1]

A. I. MEYERS AND J. M. GREENE

Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122

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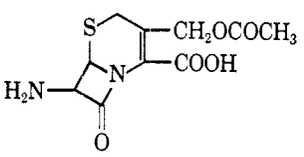
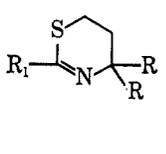
The reaction of 3-hydroxy-3-methylbutanethiol with cyanoacetic and cyanopropionic ester in boron trifluoride etherate gave good yields of the 2-carboxyalkyl-4,4-dimethyl-5,6-dihydro-1,3(4H)-thiazines (IIe and IIf). The latter were readily reduced in aqueous, mildly acidic sodium borohydride to the corresponding tetrahydro-1,3-thiazines (IIIe and IIIf). Attempts to form the β-lactam (IV) related to the cephalosporins were fruitless.

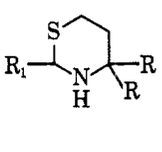
In connection with studies aimed toward the total synthesis of the antibiotic precursor, 7-aminocephalosporanic acid[2,3] (I), an investigation into the chemistry of dihydro- (II) and tetrahydrothiazines (III) was undertaken. Others[4,5] have also sought a route to the cephalosporanic acids by examining initially the chemistry of the thiazine ring system about which relatively little has been reported in recent years.[6-9] The original aim of this investigation was to prepare and characterize the related cepham system, IV. In order to obtain the latter, a pathway was chosen which began by relying on a known method[8] for preparing II (R_1 = CH_2COOEt) followed by a suitable reduction to III (R_1 = CH_2COOEt) and finally cyclization to IV. Although II and III were successfully obtained, all attempts thus far to reach IV have been fruitless. However, several novel dihydrothiazines (II) were



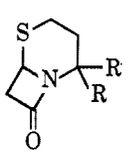
I



II



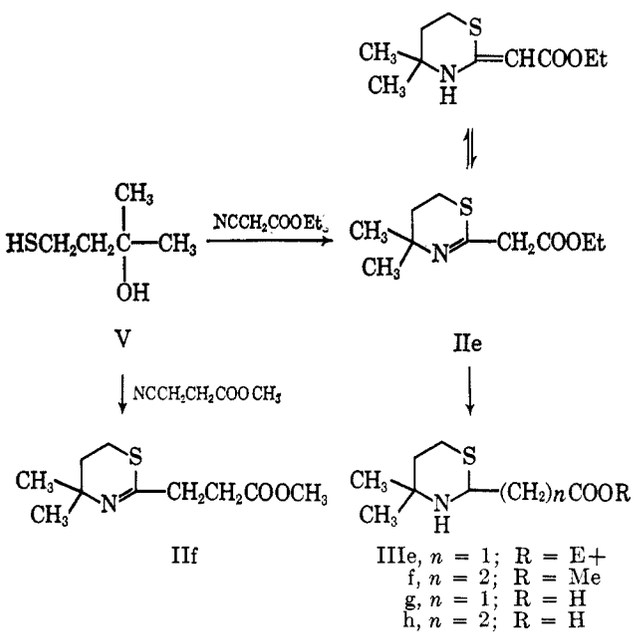
III



IV

prepared and converted to their tetrahydro derivatives (III) *via* a superior technique using sodium borohydride, and several interesting observations pertaining to thiazine chemistry were made.

By applying the thiazine synthesis[8] utilizing the mercapto alcohol V, ethyl cyanoacetate, and sulfuric acid, a 45% yield of the thiazine ester IIe was obtained. The latter was also prepared in 60% yield when the cyclization was carried out in anhydrous ether using boron trifluoride, according to Tarbell, *et al.*[10] The structure of IIe was verified by its infrared spectrum,



V IIe

IIf

IIIe, n = 1; R = E+
f, n = 2; R = Me
g, n = 1; R = H
h, n = 2; R = H

which exhibited two carbonyl bands (5.76, 6.12 μ) and an NH band (3.05 μ). These data suggested that IIe was a tautomeric mixture of the *endo* and *exo* isomers. Examination of the nmr spectrum (Figure 1) revealed a vinyl signal (τ 5.65, singlet) and an NH signal (τ 0.75) of equal area, both corresponding to 0.55 of a total proton signal. This further supports the tautomeric nature of IIe and indicates that 55% of the *exo* isomer and 45% of the *endo* isomer are present. This type of tautomerism has also been observed in 2-(carboethoxymethyl)-3,4-dihydroisoquinolines, where the *exo* isomer predominates in the ratio of 9:1.[11] The hydrochloride of IIe (Figure 1) is shown to be a single species corresponding to the *endo* isomer. This is, in part, obtained by C protonation of the *exo* isomer. This conclusion is readily supported by the absence of the vinyl signal, the sharp singlet observed for the methylene protons at the 2-position (integrated area = 2 protons), and the broad NH at τ −3.7 (integrated area = 1 proton). The infrared spectrum shows a single carbonyl band at 5.78 μ and the C=N stretch at 6.11 μ.[12] When the mercapto alcohol was

(1) This study was supported by a grant from the National Institutes of Health (AI-05611).

(2) R. B. Morin, B. G. Jackson, E. H. Flynn, and R. W. Roeske, *J. Am. Chem. Soc.*, **84**, 3400 (1962).

(3) R. R. Chauvette, *et al.*, *ibid.*, **84**, 3401 (1962).

(4) D. M. Greene, A. G. Long, P. J. May, and A. F. Turner, *J. Chem. Soc.*, 766 (1964); G. C. Barrett, V. V. Kane, and G. Lowe, *ibid.*, 783 (1964).

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(6) R. C. Elderfield and E. E. Harris, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., Interscience Publishers, Inc., New York, N. Y., 1957, p 604.

(7) R. Kuhn and F. Drawert, *Ann.*, **590**, 55 (1954).

(8) A. I. Meyers, *J. Org. Chem.*, **25**, 1147 (1960). This paper may be considered as I in this series.

(9) P. A. S. Smith and J. M. Sullivan, *ibid.*, **26**, 1132 (1961).

(10) D. S. Tarbell, D. A. Buckley, P. P. Brownlee, R. Thomas, and J. S. Todd, *ibid.*, **29**, 3314 (1964).

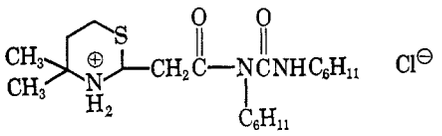
(11) W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, and A. I. Meyers, *ibid.*, **30**, 3667 (1965).

(12) A. I. Meyers, *ibid.*, **26**, 218 (1961).

treated with methyl 3-cyanopropionate in ethereal boron trifluoride there was obtained, in 57% yield, the thiazine ester IIf. This product was found to be a single isomer possessing in its infrared spectrum only a single carbonyl band (5.75 μ) and the C=N band (6.11 μ). The nmr spectrum failed to show any vinyl protons or deuterium-exchangable protons. It is therefore reasonable to conclude that conjugation with the ester carbonyl in IIe provides the driving force for its tautomeric nature.

Attempts to convert IIe to the tetrahydro derivative IIIe by catalytic hydrogenation, using platinum, palladium, and rhodium catalysts, and reductions with zinc, tin, or sodium in acids or alcohols were totally unsuccessful. The use of aqueous, mildly acidic sodium borohydride proved to be vastly superior to all other reported techniques.[13] When IIe was treated in aqueous ethanol at 0° (pH 4–6) with sodium borohydride, IIIe was isolated in 87% yield. There was no evidence of any ring-cleaved products usually observed in the thiazolidine[14] and 1,3-thiazine[15] series when metal hydrides are employed. The tetrahydrothiazine (IIIe) was identified by the absence of the C=N band in the infrared and the well-defined triplet (J = 7 cps) for the proton in the 2-position (τ 5.40). Similar treatment of the thiazine propionic ester (IIf) gave the reduced product (IIIf) in 76% yield.

With a satisfactory route to tetrahydrothiazines in hand, attention was turned to the preparation of the cepham derivative, IV. After fruitless attempts to form the β-lactam *via* aminolysis of the ester group, including the labile benzyl ester (III, R_1 = $CH_2COOCH_2C_6H_5$; R = CH_3), the thiazine acid IIIg was next considered. The acid was readily prepared as the hydrochloride by room-temperature hydrolysis of IIIe. The ring system was surprisingly stable during this hydrolysis. Treatment of the acid IIIg with thionyl or oxalyl chloride in ether, chloroform, benzene, or methylene chloride resulted in recovery of starting material. No trace of the β-lactam was evident. These procedures have been shown to be effective in closing the β-lactam ring in the penicillin series.[16,17] Employing N,N′-dicyclohexylcarbodiimide[18] in a variety of solvents and solvent mixtures also failed to produce the desired product. When this reagent and IIIg·HCl were refluxed overnight in tetrahydrofuran, a 60% yield of the thiazineurea hydrochloride (VI)



VI

was readily isolated. During an attempt to form the β-lactam from IIIg·HCl by using pyridine as a solvent, a crystalline product deposited from the solution after standing at room temperature for 12 hr. Char-

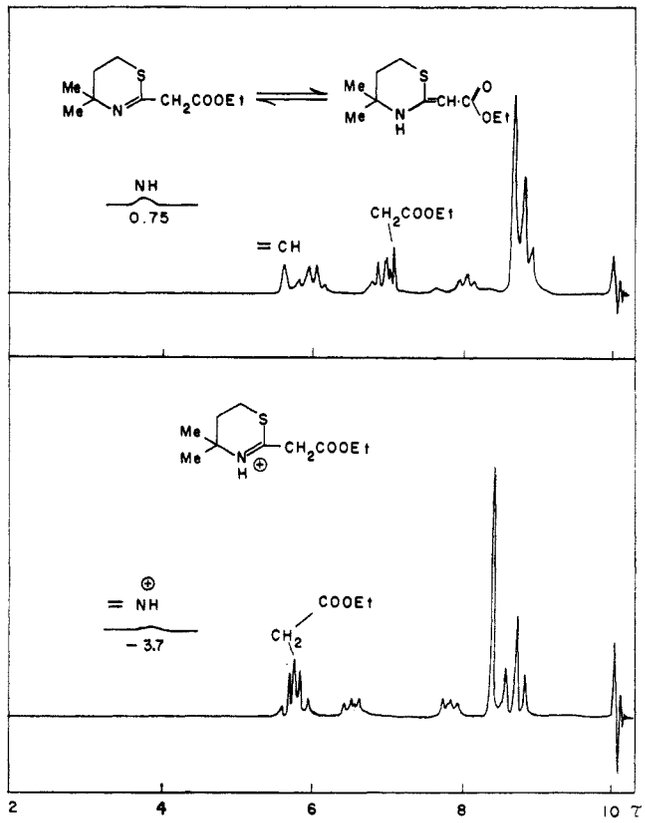
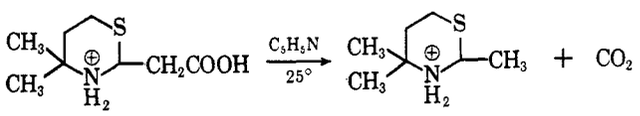


Figure 1.—Nmr spectrum of IIe in $CDCl_3$ (top) and IIe·HCl in $CDCl_3$ (bottom) at 60 Mc and 40°. Tetramethylsilane was used as internal standard.

acterization of this material unexpectedly showed it to be the 2-methylthiazine salt VII. The yield of this



IIIg VII

compound was quantitative. A search of the literature failed to provide any precedent for this unusually mild decarboxylation. When the experiment was repeated with the thiazinepropionic acid (IIIh), no decarboxylation occurred even after prolonged refluxing in pyridine. Further studies on this reaction are obviously necessary. The failure of IIIe or IIIg to cyclize to the β-lactam can, at this time, only be attributed to the hindered nitrogen on the thiazine ring and the lack of sufficient substitution[17] on the carboxymethyl side chain. Both of these possibilities are currently being evaluated in an attempt to obtain a suitable analog of IV.

Experimental Section[19,20]

2-(Carboethoxymethyl)-4,4-dimethyl-5,6-dihydro-1,3(4H)-thiazine (IIe). A. Sulfuric Acid Method.—A mixture of 24.0 g (0.2 mole) of 3-hydroxy-3-methylbutane-1-thiol[8] and 34.5 g (0.3 mole) of ethyl cyanoacetate was slowly added to 150 ml of concentrated sulfuric acid at −2 to 0°. The reaction mixture

(13) A preliminary communication has appeared: J. C. Getson, J. M. Greene, and A. I. Meyers, *J. Heterocyclic Chem.*, **1**, 300 (1964).

(14) E. L. Eliel, E. W. Della, and M. M. Rogić, *J. Org. Chem.*, **27**, 4712 (1962).

(15) E. L. Eliel and J. Roy, *ibid.*, **30**, 3092 (1965).

(16) J. C. Sheehan and D. R. Hoff, *J. Am. Chem. Soc.*, **79**, 237 (1957).

(17) J. C. Sheehan and E. J. Corey, *Org. Reactions*, **9**, 388 (1957).

(18) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **79**, 1263 (1957).

(19) All melting points are corrected. The infrared spectra were taken on a Beckman IR-5A, and the nmr spectra were taken on a Varian A-60 instrument. The nmr spectra were taken in deuteriochloroform unless otherwise indicated.

(20) The authors wish to express their gratitude to the National Science Foundation for a grant to purchase the Varian A-60 instrument (GP-1575).

was stirred for 2 hr at 3–5° and poured slowly into 400 g of chipped ice. The aqueous solution was kept between 3 and 8° during neutralization with 30% sodium hydroxide, and the resulting oil was removed by several ether extractions. The combined ethereal solutions were dried over sodium sulfate and concentrated. Distillation of the residual oil produced 18.2 g (45%) of a colorless oil: bp 110–112° (2 mm); $n^{25}D$ 1.5435; λ^{film} 3.05, 5.76, 6.12, 6.32–6.45 μ; nmr ($CDCl_3$) shown in Figure 1.

Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.81; H, 7.90; N, 6.51. Found: C, 55.68; H, 7.95; N, 6.68.

The **picrate**, recrystallized from ethanol, had mp 137–138°.

Anal. Calcd for $C_{16}H_{20}N_4O_9S$: C, 43.24; H, 4.50; N, 12.61. Found: C, 43.49; H, 4.50; N, 12.33.

The **hydrochloride** (from ethanol–ether, 1:1) was prepared by passing hydrogen chloride into an ethereal solution of IIe, mp 196–197°.

Anal. Calcd for $C_{10}H_{18}ClNO_2S$: C, 47.71; H, 7.16; Cl, 14.11; N, 5.56; S, 12.72. Found: C, 47.90; H, 7.21; Cl, 14.26; N, 5.63; S, 12.88.

B. Boron Trifluoride Method.—A solution of 12.09 g (0.1 mole) of 3-hydroxy-3-methylbutane-1-thiol, 16.0 g (0.14 mole) of ethyl cyanoacetate, and 60 ml of freshly distilled boron trifluoride etherate in 200 ml of dry ether was flushed with nitrogen and allowed to stand at room temperature for 7 days. The solvent was removed under aspirator pressure, and 200 ml of water was added to the residue. Any water-insoluble material was removed by ether extraction. The aqueous solution was rendered slightly alkaline with 5% sodium carbonate solution and the resulting oil was removed by ether extraction. Drying and concentration of the ethereal solution produced an oil which upon distillation gave 12.8 g (59%) of the thiazine ester IIe.

2-(2-Carbomethoxyethyl)-4,4-dimethyl-5,6-dihydro-1,3(4H)-thiazine (IIf).—A solution of 12.0 g (0.1 mole) of 3-hydroxy-3-methyl-*n*-butanethiol, 16.0 g (0.14 mole) of methyl 3-cyanopropionate, 60 ml of boron trifluoride etherate in 200 ml of anhydrous ether was flushed with nitrogen and allowed to stand for 10 days at room temperature. The ether solution was extracted four times with 75-ml portions of cold water and the aqueous extracts were neutralized with 5% sodium carbonate. The oil which separated was extracted with ether and the extracts were dried (sodium sulfate) and concentrated. Distillation of the concentrate gave 12.2 g (57%) of a colorless oil: bp 90–92° (0.4 mm); $n^{25}D$ 1.4972; λ^{film} 5.75, 6.11 μ; τ^{neat} 8.99 (*gem*-CH_3), 8.42 (5-H), 7.48 ($-CH_2CH_2CO-$), 6.95 (6-H), 4.41 (OCH_3).

Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.81; H, 7.90; N, 6.51; S, 14.88. Found: C, 55.56; H, 8.12; N, 6.50; S, 14.73.

2-(Carbobenzyloxymethyl)-4,4-dimethyl-5,6-dihydro-1,3(4H)-thiazine.—A solution of 10 g of IIe in 100 ml of benzyl alcohol containing 0.2 g of sodium was refluxed for 12 hr, and then the solvent was partially removed by distillation at atmospheric pressure. The benzyl alcohol solution was shaken with 10% hydrochloric acid and the latter solution was neutralized to free the thiazine benzyl ester, mp 79–80°.

Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.98; H, 6.86; N, 5.05; S, 11.55. Found: C, 65.09; H, 6.90; N, 5.03; S, 11.73.

Formation of Tetrahydro-1,3-thiazines IIIe and IIIf Using Sodium Borohydride.—The apparatus consisted of a 400–600-ml beaker immersed in an ice bath. The beaker was fitted with an overhead stirrer motor, thermometer, pH electrodes, and two 50-ml burets which were adjusted so that the reagents were readily introduced into the beaker. The thiazine ester (0.1 mole) was dissolved in 200 ml of 50% aqueous ethanol and 3 *N* hydrochloric acid added to adjust the pH to 5. The solution was cooled to 0° and a slightly alkaline solution of sodium borohydride (0.3–0.5 moles in 50 ml of water containing 1–2 drops of 30% sodium hydroxide) was added dropwise from one buret. The rate of addition was adjusted so that the temperature did not exceed 0°. The pH was continuously monitored and was maintained between 4–6 by the periodic additions of 3 *N* hydrochloric acid from the second buret. The addition of hydride required 1–2 hr after which the mixture was stirred for 30 min and then diluted with 300 ml of water. After adjusting the pH to 9–10, the solution was extracted four or five times with ether, and the combined extracts were dried over sodium sulfate and concentrated. The residual crude tetrahydrothiazine esters were then distilled.

IIIe was obtained in 87% yield: bp 91–92° (0.6 mm), $n^{25}D$ 1.4966, picrate (from ethanol) mp 134–135°.

Anal. Calcd for $C_{10}H_{19}NO_2S$: C, 55.28; H, 8.75; N, 6.45. Found: C, 55.48; H, 8.72; N, 6.67.

IIIf was obtained in 76% yield: bp 122–124° (1.5 mm), $n^{25}D$ 1.4994, hydrochloride mp 194°.

Anal. Calcd for $C_{10}H_{19}NO_2S$: C, 55.28; H, 8.75; N, 6.45. Found: C, 55.10; H, 8.93; N, 6.38.

Decarboxylation of IIIg·HCl to IIIc.—A solution of 0.5 g of IIIg·HCl in 20 ml of pyridine was allowed to stand at room temperature for 12 hr. The precipitate (0.41 g) was collected by filtration and recrystallized from ethanol–ether (1:1). The product (IX, 0.40 g) did not melt but rapidly sublimed above 200°: τ^{D_2O} 8.58, 8.62 (*gem*-methyls), 8.47 (doublet, J = 7 cps, 2-CH_3), 5.35 (quartet, 2-H).

Anal. Calcd for $C_7H_{16}ClNS$: C, 46.24; H, 8.88; N, 7.71; S, 17.65. Found: C, 45.96; H, 8.70; N, 7.79; S, 18.10.

The above hydrochloride was decomposed in 0.1 *N* sodium hydroxide solution and the latter was extracted with ether. After drying and concentration, the residue was treated with alcoholic picric acid. The melting point (196°) was undepressed upon admixture with the picrate prepared directly from IIIc.

2-(Carboxymethyl)-4.4-dimethyltetrahydro-1,3-thiazine (IIIg·HCl).—A solution of 8.3 g (0.038 mole) of IIIe in 175 ml of cold concentrated hydrochloric acid was stirred for 1 hr, and 50 ml of water was then added. The solution was stirred for 12 hr, and the solvent was removed *in vacuo*. The residual solid (7.9 g) was recrystallized from ethanol–ether (1:1) to give 7.5 g of pure product: mp 245°; τ^{D_2O} 8.52 (*gem*-methyls), 5.01 (triplet, J = 7 cps, 2-H).

Anal. Calcd for $C_8H_{16}ClNO_2S$: C, 42.54; H, 7.28; Cl, 15.93; N, 6.22; S, 14.41. Found: C, 42.56; H, 7.14; Cl, 15.75; N, 6.21; S, 14.22.

2-(2-Carboxyethyl)-4,4-dimethyltetrahydro-1,3-thiazine (IIIh·HCl).—A solution of 7.6 g of IIIf in 175 ml of concentrated hydrochloric acid was stirred for 18 hr at room temperature. After evaporation *in vacuo* of the solvent, the resulting crystalline residue (7.1 g) was washed several times with hot acetonitrile and dried: mp 253°; τ^{D_2O} 8.58, 8.62 (*gem*-methyls), 5.40 (triplet, J = 6.6 cps, 2-H).

Anal. Calcd for $C_9H_{15}ClNO_2S$: C, 45.06; H, 7.57; Cl, 14.79; N, 5.85; S, 13.38. Found: C, 44.87; H, 7.52; Cl, 14.84; N, 5.64; S, 13.55.

Attempted Cyclization of IIIg·HCl to IV (Dicyclohexylcarbodiimide).—A suspension of 2.0 g (0.008 mole) of IIIg·HCl was refluxed for 12 hr in 200 ml of a solution of dicyclohexylcarbodiimide (1.8 g, 0.009 mole) in tetrahydrofuran. The suspended solid was collected by filtration and, after drying *in vacuo*, melted at 194–196°. The crystalline product, 2.25 g (59.6%), was repeatedly washed with tetrahydrofuran, since it could not be satisfactorily recrystallized. The infrared spectrum (Nujol) exhibited peaks at 2.95, 6.12, 6.30, and 6.51 μ. The product was assigned the structure of the substituted urea, VIII, as its hydrochloride salt.

Anal. Calcd for $C_{21}H_{38}ClN_3O_2S$: C, 58.38; H, 8.87; N, 9.73; S, 7.42. Found: C, 58.52; H, 9.08; N, 9.78; S, 7.60.