Synthesis of 2′-(2-Aminoethyl)-2,4′-bithiazole-4-carboxylic Acid, A Component of the Antitumor Antibiotic Bleomycin (1)

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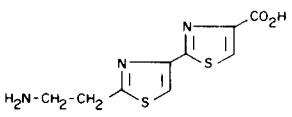
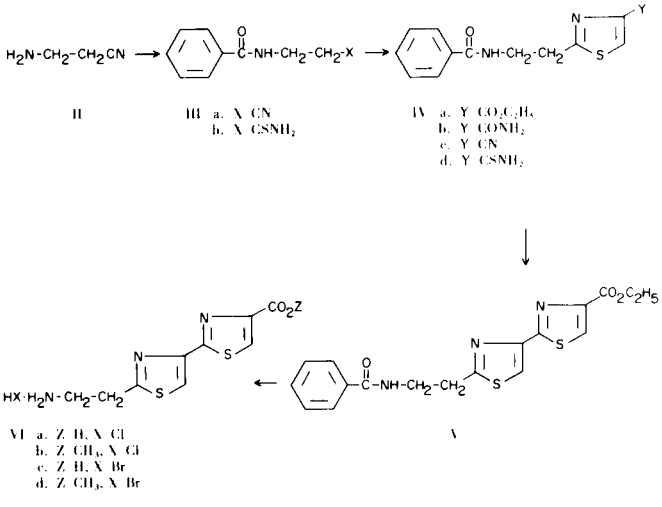
Sir:

During the past decade, the 2,4′-bithiazole unit has repeatedly been shown to occur in a number of antibiotics such as micrococcin P, saramycetin and bleomycin (2-10). This unique system which constitutes the backbone of these compounds, is believed to play a role in the biological activity of these natural products. Recently, the structure of one of the acid hydrolysis products of the antitumor antibiotic bleomycin (11-15) was shown by X-ray analysis (9) to be 2′-(2-aminoethyl)-2,4′-bithiazole-4-carboxylic acid (I). Since biogenetically compound I can be visualized as being derived from one molecule of β-alanine and two molecules of cysteine, in connection with our study of biologically active sulfur-containing amino acids (16) and peptides (17), synthesis of compound I was initiated.



I

Compound I has now been obtained from 3-aminopropionitrile (II) *via* the following route in 26-30% overall yield. Benzoylation of II gave 88%-to-quantitative yield of the benzoylated compound IIIa, m.p. 94-96°; λ max (ethanol) 226 mμ (log ε 4.11). Treatment of IIIa with hydrogen sulfide in dimethylformamide in the presence of diethylamine, using a modified procedure of Gilbert, *et al.* (18), afforded an 84% yield of the corresponding thioamide IIIb, m.p. 170-171°; λ max (ethanol) 267 mμ (log ε 4.12). Condensation of IIIb with ethyl bromopyruvate gave an 88% yield of ethyl 2-(2-benzamidoethyl)-thiazole-4-carboxylate IVa, m.p. 112-113°; λ max (ethanol) 230 mμ (log ε 4.28). The corresponding amide IVb, m.p. 131-133°, was obtained in near quantitative yield from IVa and methanolic ammonia at 110° in a pressured vessel. Dehydration of IVb with phosphorus oxychloride in pyridine gave a 60% yield of the nitrile IVc, m.p. 125-127°. Compound IVc was converted to the thioamide IVd with hydrogen sulfide (m.p. 144-146°, 84% yield), which was then condensed with ethyl bromopyruvate to give a 93% yield of ethyl 2′-(2-benzamidoethyl)-2,4′-bithiazole-4-carboxylate (V), m.p. 143-145°; λ max (ethanol) 290 mμ (log ε 4.18). Acid hydrolysis of V with 20% hydrochloric acid gave near quantitative yield of the dihydrochloride salt of 2′-(2-aminoethyl)-2,4′-bithiazole-4-carboxylic acid, which, upon recrystallization from methanol and ethyl acetate, gave a 95% yield of the monohydrochloride salt VIa, m.p. 268-270°; λ max (ethanol) 290 mμ (log ε 4.16). Esterification of VIa with 2,2-dimethoxypropane (19) in the presence of concentrated hydrochloric acid yielded the corresponding methyl ester VIb, m.p. 236-237°; λ max (ethanol) 289 mμ (log ε 4.14). The corresponding hydrobromide salt VIc was obtained in a similar fashion, m.p. 272-274°. The hydrobromide salt of the methyl ester of 2′-(2-aminoethyl)-2,4′-bithiazole-4-carboxylic acid (VId), was readily prepared from VIb, m.p. 241-242° [lit. (9), m.p. 233-233.5° for the monohydrate of VId]; λ max (*p*H 1) 289 mμ (log ε 4.16). Elemental analyses of all compounds reported in this communication have been performed and were found to be within 0.3% of the theoretical values.



II

III a. X CN
b. X $CSNH_2$

IV a. Y $CO_2C_2H_5$
b. Y $CONH_2$
c. Y CN
d. Y $CSNH_2$

V

VI a. Z H, X Cl
b. Z CH_3, X Cl
c. Z H, X Br
d. Z CH_3, X Br

REFERENCES

(1) This investigation was supported by Contract No. PH-43-65-94 with Chemotherapy, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) P. Brookes, R. J. Clark, A. T. Fuller, M. P. V. Mijović, and J. Walker, *J. Chem. Soc.*, 916 (1960).

(3) P. Brookes, R. J. Clark, B. Majhofer, M. P. V. Mijović, and J. Walker, *ibid.*, 925 (1960).

(4) R. J. Clark and J. Walker, *J. Chem. Soc.* (C), 1354 (1966).

(5) M. N. G. James and K. J. Watson, *ibid.*, 1361 (1966).

(6) G. E. Hall, N. Sheppard, and J. Walker, *ibid.*, 1371 (1966).

(7) A. Aszalos, A. I. Cohen, J. Alicino, and B. T. Keeler, *Antimicrobial Agents Chemotherapy*, 456 (1967).

(8) T. Takita, Y. Muraoka, K. Maeda, and H. Umezawa, *J. Antibiotics*, 21, 79 (1968).

(9) G. Koyama, H. Nakamura, Y. Muraoka, T. Takita, K. Maeda, and H. Umezawa, *Tetrahedron Letters*, 4635 (1968).

(10) T. Takita, Y. Muraoka, S. Omoto, G. Koyama, A. Fujii, K. Maeda, and H. Umezawa, *Progr. Antimicrobial Anticancer Chemotherapy*, Vol. II, University of Tokyo Press, 1969, p. 1031.

(11) Bleomycin is a collective name of thirteen different antibiotics. The bithiazole unit is present in at least five of these (bleomycin A_2, A'_2, B_2, A_5 and A_6).

(12) A. Matsuda, K. Miyamoto, M. Tsubosaki, T. Kaihara, K. Sakamoto, and H. Umezawa, *J. Antibiotics*, 20, 149 (1967).

(13) H. Suzuki, K. Nagai, H. Yamaki, N. Tanaka, and H. Umezawa, *ibid.*, 21, 379 (1968).

(14) T. Ichikawa, *J. Japan Med. Assoc.*, 61, 487 (1969).

(15) K. Takeda, Y. Sagawa, and T. Arakawa, *Gann*, 61, 207 (1970).

(16) K. Y. Zee-Cheng and C. C. Cheng, *J. Med. Chem.*, 13, 414 (1970).

(17) K. Y. Zee-Cheng and C. C. Cheng, unpublished work.

(18) E. E. Gilbert, E. J. Ramanowski, and P. E. Newallis, *J. Chem. Eng. Data.*, 13, 130 (1968).

(19) J. R. Rachele, *J. Org. Chem.*, 28, 2898 (1963).

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