THE SYNTHESIS OF SULFOMYCININE

Hiroshi Abe, Tetsuo Takaishi and Yukio Ito

Microbiological Department,

Biological and Chemical Research Laboratories,

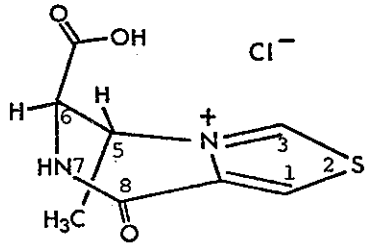
Tomoharu Okuda*

Research Administration Division,

Tanabe Seiyaku Co., Ltd. Toda, Saitama, Japan

The structure and configuration of sulfomycinine, one of the acid degradation products of an antibiotic sulfomycin I, was communicated previously. In this communication, synthesis of sulfomycinine is reported.

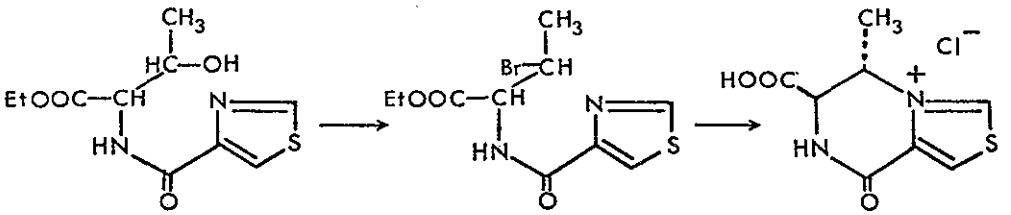
Sulfomycinine hydrochrolide (I)[1] [$C_8H_8N_2O_3S \cdot HCl$; mp 205-207°C (dec.), ir (KBr) 3100, 1740, 1695 cm^{-1}] obtained as a racemic mixture by acid hydrolysis of sulfomycin I[2] was assumed to be 6-carboxy-5-methyl-8-oxo-5,6,7,8-tetrahydrothiazolo[3,4-a]pyrazinium chloride.



I Sulfomycinine hydrochloride

Starting from DL-threonine and DL-allothreonine, synthetic sulfomycinine possessing the same configulation with authentic I has been successfully obtained by the procedures shown in Fig. 1, in which N-alkylation by the intramolecular cyclization was involved. Compounds IIa-c, ethyl 3-hydroxy-2-(4-thiazolylcarboxamido)butyrate, were obtained quantitatively by coupling 4-thiazolecarbonyl chloride with DL-, L-threonine and DL-allothreonine ethylester, respectively, in dichloromethane containing triethylamine.

Fig. 1



	mp		yield		mp	yield
IIa	110-112°C	IIIa	62.1%	IVa	206-208°C	8.3%
b	129-130°C	b	64.1%	b	219-220°C	7.5%
c	106-108°C	c	60.7%	c	205-207°C	5.8%

Bromo derivatives (IIIa-c) were prepared from IIa-c, respectively, by treating IIa-c (1 mole) with N-bromosuccinimide (2 moles) and triphenylphosphine (2 moles) in dichloromethane at room temperature for 3 hrs[3]. Compounds IIIa-c were purified by silica gel column chromatography developed with chloroform. Though IIIa-c thus obtained were oily, very unstable and readily colored, their structures were confirmed by ir and mass spectrometry [*m/e* 322, 320 (M^+), 277, 275 (M^+-OEt), 249, 247 (M^+-COOEt)]. After IIIa-c were heated for 3 hrs in neat in the presence of small amounts of sodium iodide in an oil bath kept at 150°C, the reaction mixture was heated with

hydrochloric acid for complete de-esterification, though the ethyl ester was partly hydrolyzed during pyrolysis. The synthetic IVa-c thus obtained were purified by Sephadex LH-20 column chromatography developed with water and crystallized respectively as hydrochlorides with the aid of hydrochloric acid in ethyl alcohol.

Among synthetic IVa-c, IVa and IVc were confirmed to be identical with I in all respects of physicochemical properties. The nmr spectrum of IVb was identical with that of I and also with IVa,c. However, IVb was optically active and could be distinguished from I in the following properties, IVb: mp 219-220°C (dec.), ir (KBr) 1710, 1690, 1210 cm^{-1}, $[\alpha]_D^{20}$ +139° (c=1, H_2O).

No compound possessing the 5,6-*cis* configuration was obtained or isolated from the cyclization mixture, even in the reaction product started from DL-allothreonine. Therefore, the present result suggested that cyclization took place so as to give a thermodinamically stable 5,6-*trans* isomer. As an alternative trial, N-alkylation of 4-thiazolecarboxylic acid by an appropriate alkyl bromide which will be followed by lactamization was attempted, but this trial was failed.

REFERENCES

1) H. Abe, M. Ikeda, T. Takaishi, Y. Ito and T. Okuda, Tetrahedron Lett., 1977, 735.

2) Y. Egawa, K. Umino, Y. Tamura, Y. Shimizu, K. Kaneko, M. Sakurazawa, S. Awataguchi and T. Okuda, J. Antibiotics, 1969, 22, 12.

3) A.K. Bose and B. Lal, Tetrahedron Lett., 1973, 3937.

Received, 5th August, 1977