CCA-708 615.779.07
Preliminary Communication

Thiazabicycloheptenones. Synthesis of Bicyclic Thiazoline Azetidinone Derivatives*

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Received December 27, 1971

Chlorinolysis of the S_1—C_5 bond in penicillin G and the subsequent cyclization of the obtained product to the thiazabicycloheptenone is described. The intermediate azetidinone imidoyl chloride III is prepared by treatment of the olefinic azetidinone II with phosphorous pentachloride. Cyclization of III is effected with thioacetate anion or hydrogen sulfide in the presence of triethylamine.

The structure and chirality of thiazabicycloheptenone IV were established by spectral data as well as by comparison with the sample prepared by an independent manner[3] from penicillin G sulfoxide.

We have recently reported new reactions involving the electrophilic opening of the penicillin molecule and subsequent ring closure of the products to 5-epipenicillins[1]. These reactions were reported only with 6-phthalimidopenicillanates. However, the electrophilic opening of the thiazolidine ring has since been carried out with penicillins having in the side chain amide group, *e. g.*, penicillin G. Cleavage of the S_1—C_5 bond of the thiazolidine ring in penicillin G and ring closure of the product to a bicyclic thiazolidine azetidinone is described in this paper.

Chlorinolysis of trichloroethyl 6-phenylacetamidopenicillanate (I)[2] with 2.8 equiv of chlorine in methylene chloride at — 76° for 90 min and at room temp. for an additional 30 min. gives 2*S*-chloro-3*R*-phenylacetamido-1-(1′-*S*-trichloroethyloxycarbonyl-2′-methyl-prop-1′-enyl)azetidine-4-one (II) as the sole product. The *trans* isomer II is isolated as an amorphous solid in $> 90\%$ yield after workup, and the structural assignment is based on elemental analysis and spectral data as outlined previously[1a].

Treatment of II with 1.1 equiv of phosphorus pentachloride and quinoline in dry chloroform at — 10° for 30 min affords the imidoyl chloride III as an oil in $> 75\%$ yield. The IR spectrum of III shows the absence of amide carbonyl absorption at 1685 cm^{-1} and indicates the presence of the azetidinone (1788) and ester (1735 cm^{-1}) groups. Furthermore, the structure of III is supported by chemical shift values of the side chain methylene and azetidinone protons situated adjacent to the imidoyl chloride group. Due to the electronegative character of this group, protons in the immediate vicinity show the expected downfield shift (see Table I). Additional proof of the structure is also obtained by hydrolysis of III to the starting amide II.

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* Azetidinone Antibiotics. III. Ref. 1a and 1b may be considered as Part I and II in this series.

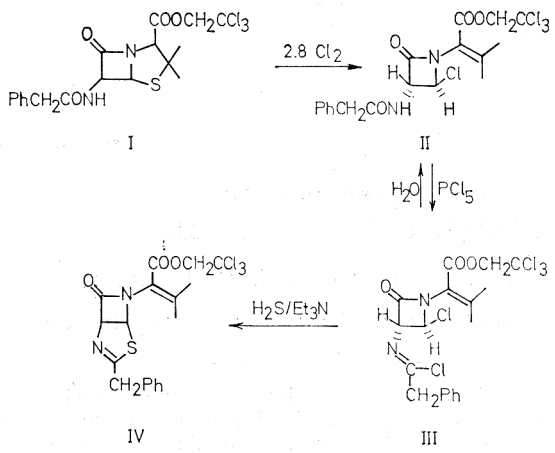


TABLE I

NMR Chemical Shift Values ($CDCl_3$)[a]

Compound	$=CMe_2$	$PhCH_2$-	Ester $-CH_2$-	H_3	H_2	Arom H
II	125,142	227	286 (q, J = 6, 12)	304 (q, J = 1.5, 8)	352 (d, J = 1.5)	439
III	126,144	236	288 (q, J = 8, 14)	314 (d, J = 2)	364 (d, J = 2)	421
IV	100,135	233	296 (q, J = 8, 11)	359[b] (s)	359[b] (s)	421

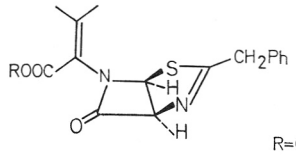
[a]Chemical shift and J values in Hz. Measured on a Varian HA-60 using TMS as internal reference.

[b]Protons H_2 and H_3 appear as a quartet in trifluoracetic acid-*d*. A similar solvent dependency has been noted for compound of this type by Copper and José[3]

Cyclization of III with hydrogen sulfide or thiolacetic acid in methylene chloride in the presence of triethylamine at room temperature for 1 hr followed by chromatography on silica gel yields bicyclic thiazoline azetidinone IV (30%) as a colorless oil: $[\alpha]_D$ + 12.5° ($CHCl_3$), IR ($CHCl_3$) 1735 cm^{-1} and 1768 cm^{-1}. The ease with which the imidoyl chloride III cyclizes to IV can be ascribed to the fact that the rigid azetidinone ring holds the reacting groups in proximity.

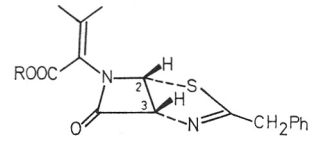
Although we had established the structure of IV on the basis of spectral data (see Table I) there was still some ambiguity about the stereochemistry of the bicyclic system. The question of stereochemistry arises when one considers the reaction conditions under which the thiazabicycloheptenone IV is formed. Since the electron withdrawing imidoyl group in III increases the acidity of the hydrogen on carbon 3, the use of triethylamine* could result in abstraction of that proton and subsequent epimerization of the chiral center 3. Therefore, either of the isomers (2 *S*, 3 *S*) V and (2 *R*, 3 *R*) VI are possible products.

* When the reaction of III with hydrogen sulfide or thiolacetic acid is carried out without base, the starting imidoyl chloride is recovered.



V

R=CH_2CCl_3



VI

In order to substantiate the structure of IV and to establish the chirality, the same compound has been prepared according to the method of Cooper and José[3]. Treatment of trichloroethyl penicillin G sulfoxide with trimethylphosphite in boiling benzene for 48 hr and the subsequent isomerization of double bond with triethylamine gives a thiazabicycloheptenone having $[\alpha]_D$ + + 10.9°, and also identical in spectral properties to the compound IV. Since Cooper and José[3,4] have established the absolute configuration of thiazoline azetidinones obtained by rearrangement of penicillin sulfoxides, compound IV might be expected to exist as depicted by VI.

The successful application of chlorinolysis to penicillin G esters demonstrates some generality of this reaction to other penicillins. Further studies on the utility of described compounds are in progress.

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4. R. D. G. Cooper, unpublished results.

IZVOD

Tiazabicikloheptenoni. Sinteza bicikličkih tiazolin azetidinon derivata

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Opisano je cijepanje S_1—C_5 veza u penicilinu G i naknadna ciklizacija dobivenog produkta u tiazabicikloheptenon. Azetidin imidoil klorid III pripravljen je reakcijom olefinskog azetidinona II s fosfornim pentakloridom. Ciklizacija spoja III uspješno je provedena s tiolacetatnim anionom ili pomoću H_2S u prisutnosti trietilamina.

Struktura i konfiguracija tiazabicikloheptenona IV utvrđena je na osnovu spektralnih svojstava, a također i usporedbom s autentičnim uzorkom pripravljenim po metodi prethodno opisanoj u literaturi.

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Primljeno 27. prosinca 1971.