PREPARATION OF 7-SPIROEPOXY AND 7,7-DISUBSTITUTED CEPHALOSPORANATE 1,1-DIOXIDE FROM 7-DIAZOCEPHALOSPORANATE 1,1-DIOXIDE: REACTIONS OF 7-DIAZOCEPHALOSPORANATE 1,1-DIOXIDE WITH ALDEHYDES

David CZAJKOWSKI, Oludotun A. PHILLIPS, Narender A. V. REDDY, Paul SPEVAK, Bruce LIX, Ronald G. MICETICH and Samarendra N. MAITI*

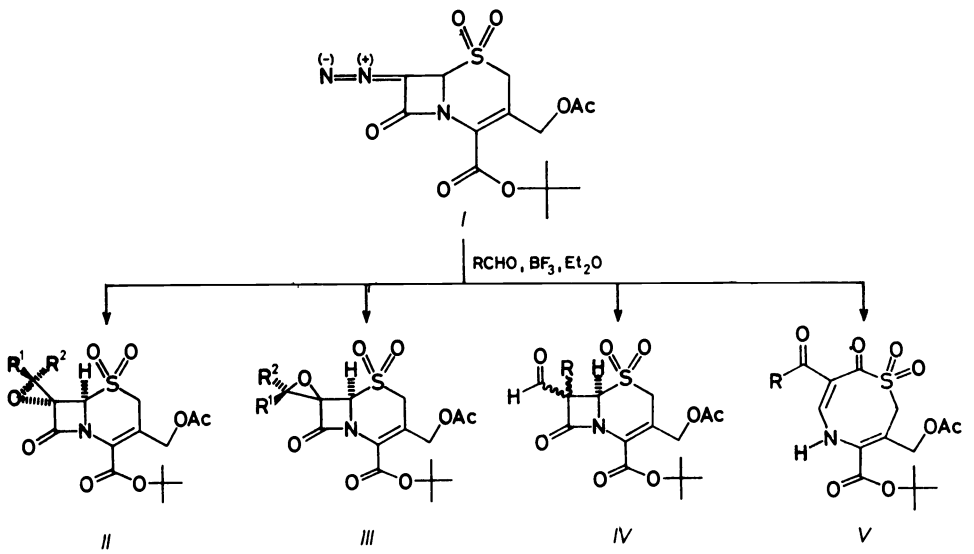
SynPhar Laboratories Inc., No. 24, 4290-91A St., Taiho Alberta Centre, Edmonton, Alberta, Canada T6E 5V2

Received December 18, 1990
Accepted February 13, 1991

Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

The reactions of tert-butyl 3-acetoxymethyl-3-cephem-7-diazocephalosporanate 1,1-dioxide (*I*) with acetaldehyde, benzaldehyde, 2-thiophene carboxaldehyde, 3-thiophene carboxaldehyde, 2-furan carboxaldehyde, 3-furan carboxaldehyde and isobutyraldehyde have been studied. Use of boron trifluoride etherate as a catalyst for these reactions was found to accelerate the reactions markedly and to favour the formation of aldehydes rather than the ketones at C-7 position as the carbonyl product. The products obtained from these reactions and the ratios of carbonyl products to epoxides suggest that the R groups of the carbonyl component have profound influence on the reactions.

6-Diazopenicillanates and 7-diazocephalosporanates have been extensively exploited in the formation of a range of modified β-lactams[1-11]. The use of esters of 7-diazocephalosporanic acid for the introduction of 7α-substituent into the cephem nucleus has been of great importance, as shown by a rapidly increasing number of patents and publications[12-15]. As part of a general program to further investigate the properties of this readily available, potential reactive intermediate, the reaction of tert-butyl 3-acetoxymethyl-3-cephem-7-diazocephalosporanate 1,1-dioxide (*I*) with a range of aldehydes was undertaken. It is known that diazoalkanes undergo reactions with carbonyl compounds to give epoxides, ketones and other rearranged products[16]. During the course of our studies on the reaction between the 7-diazocephalosporanate 1,1-dioxide *I* and various aldehydes it was noticed that if the reaction was carried out using a slight excess of aldehyde in dichloromethane with boron trifluoride etherate as catalyst, then two major products were formed in addition to other minor products. On the basis of their ^{1}H NMR and ^{13}C NMR spectra the major products were identified as 7-spiroepoxy cephalosporanate 1,1-dioxides *II* and 7,7-disubstituted cephalosporanate 1,1-dioxides *IV* (Scheme 1).



In formulae *II* and *III*: *a*, $R^1 = R$, $R^2 = H$; *b*, $R^1 = H$, $R^2 = R$

In formulae *II*–*V*: R = 3-thienyl, 2-thienyl, 3-furyl, 2-furyl, phenyl, methyl, 2-propyl

SCHEME 1

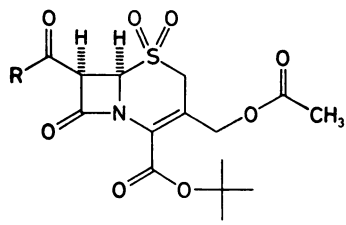
RESULTS AND DISCUSSION

Addition of boron trifluoride etherate to a solution of 7-diazocephalosporanate 1,1-dioxide *I* and a slight excess of 3-thiophene carboxaldehyde in anhydrous dichloromethane resulted in the rapid evolution of nitrogen, and led to the formation of four isolable products (Scheme 1) which were separated by repeated column chromatography and preparative TLC and tentatively identified as three isomeric epoxides and one carbonyl product. Although four isomeric epoxides (*IIa*, *IIb*, *IIIa* and *IIIb*) are expected from this reaction, the fourth isomeric epoxide was not isolated from this reaction (however, the ^{1}H NMR of the crude reaction mixture showed signals attributable to four isomeric epoxides). It is probable that the other isomeric epoxide was produced in this reaction but was not isolable because of poor yield. The epoxide present in largest amount is tentatively identified as 7α-spiroepoxy cephalosporanate 1,1-dioxide *IIa* (R_1 = R = 3-thienyl, R_2 = H) on the basis of an elemental analysis compatible with a $C_{19}H_{21}NO_8S_2$ formula and ^{1}H and ^{13}C NMR spectrum which are compatible with the assigned structure. The stereochemistry of the epoxide ring is not absolutely established, it is assumed that the aldehyde approaches preferentially from the least hindered α-face of the cephalosporanate

thus accounting for the α-epoxide as the major product. Though the configuration at the 3′-position of the epoxide ring is not known, preferred orientation would be with the R group pointing away from the sulfone moiety, since there would be considerable steric hindrance between the R group of the aldehyde and the sulfone moiety in the opposite orientation.

The ^{13}C NMR spectrum of the 7-spiroepoxide product *IIa* (R = 3-thienyl) revealed only three carbonyl signals (158·98, 161·57, and 170·33) and a signal (65·82) assignable to the quaternary carbon of the spiro epoxide. The compound present in larger amount is identified as 7-formyl-7-(3-thienyl)-3-acetoxymethyl-3-cephem 1,1-dioxide (*IV*, R = 3-thienyl) on the basis of ^{1}H NMR spectrum which shows a singlet at δ 9·83 accounting for one proton, attached to the aldehyde carbonyl.

The third product is tentatively identified as 7β-spiroepoxy cephalosporanate 1,1-dioxide *IIIa* (R_1 = R = 3-thienyl, R_2 = H) on the basis of its ^{1}H and ^{13}C NMR spectrum. The main spectral dissimilarity between the α-epoxide *IIa* and the β-epoxide (*IIIa*) appeared in the ^{1}H NMR signals of their epoxide proton and C-6 proton. In the case of α-epoxide the C-6 proton appeared as a broad doublet at δ 4·72 with a small coupling constant ($J \sim 1{\cdot}2$ Hz, $\phi \simeq 36{\cdot}6°$) while the C-6 proton of the β-epoxide appeared as a distinct doublet at δ 4·98, with a large coupling constant ($J = 5{\cdot}5$ Hz, $\phi \simeq 3{\cdot}5°$). Though the large coupling constant ($J = 5{\cdot}5$ Hz) might suggest the presence of a β-substituted ketonic product as represented by the structure *VI* (R = 3-thienyl), the possibility that the compound *IIIa* is not a ketone was ruled out on the basis of its ^{13}C NMR spectrum.



VI, R = 3-thienyl

Had the ketonic product *VI* (R = 3-thienyl) been present, it should have been shown four carbonyl signals, instead it showed only three signals at δ 159·2, 162·56, and 170·38, respectively. The component present in smallest amount is tentatively identified as 7-spiroepoxide product on the basis of its ^{1}H NMR spectrum which exhibited a doublet at δ 5·32 ($J = 2{\cdot}0$ Hz) and a poorly resolved triplet at δ 5·44 accounting for one proton. At this stage configuration at the spiroepoxide ring cannot be assigned for this isomeric epoxide. When tert-butyl 7-diazocephalosporanate 1,1-dioxide (*I*) was dissolved in a solution of 2-thiophene carboxaldehyde

in methylene chloride containing boron trifluoride etherate, rapid evolution of nitrogen occurred and two β-lactam containing products (Scheme 1) could be isolated by chromatography on silica. These proved to be the spiro epoxides *IIa* (R_1 = R = = 2-thienyl) and *IIIa* (R_1 = R = 2-thienyl) in yields of 13% and 3%, respectively. The structure of the 7α-spiroepoxide *IIa* (R_1 = R = 2-thienyl) followed from its ^{1}H NMR spectrum which revealed the presence of two doublets with small coupling constants (δ 4·76, d, J = 1·7 Hz, and δ 5·23, d, J = 1·9 Hz). The configuration of the epoxide ring at C-7 position and the stereochemistry at the 3'-position of the epoxide ring were assumed on the basis of the explanation as described for the previous example. To the other component, more polar than *IIa*, we have assigned the structure *IIIa* (R_1 = R = 2-thienyl) based on the spectroscopic data. The stereochemistry at C-7 was assigned on the basis of the coupling between the epoxide proton and C-6 proton of the β-lactam ring. The 7β-spiroepoxide had coupling constants of 5·4 Hz whereas the 7α-spiroepoxide had coupling constant of about 2·0 Hz. Although the formation of 7β-spiroepoxide is consistent with the analogous reaction described before, during the purification of 7β-spiroepoxide *IIIa* (R_1 = = R = 2-thienyl) on silica TLC plates an unexpected finding was observed; the 7β-spiroepoxide rearranges slowly to the thermodynamically more stable 7α-spiroepoxide *IIa* (R_1 = R = 2-thienyl) and the conversion was complete when the 7β-spiroepoxide was stirred for 48 h at room temperature with silica gel in dry methylene chloride. The differing behaviour of the two 7β-spiroepoxides, *IIIa* (R_1 = R = 2-thienyl) and *IIIa* (R_1 = R = 3-thienyl) is not entirely clear. Indeed the analogous phenyl substituted 7β-spiroepoxide *IIIa* (R_1 = R = phenyl) does rearrange to the 7α-spiroepoxide *IIa* (R_1 = R = phenyl) in presence of silica gel. Next $BF_3.Et_2O$ catalyzed reaction between the tert-butyl 7-diazocephalosporanate 1,1-dioxide (*I*) and isobutyraldehyde was examined. From this reaction two β-lactam containing products and a non β-lactam product (Scheme 1) were isolated. The compound present in largest amount is identified as tert-butyl 7-formyl-7-isopropyl--3-acetoxymethyl cephalosporanate 1,1-dioxide (*IV*, R = isopropyl) on the basis of an elemental analysis compatible with a $C_{18}H_{25}NO_8S$ formula, its ^{1}H NMR spectrum which shows a singlet at δ 9·93 accounting for one proton attached to the aldehyde carbonyl; its ^{13}C NMR spectrum showed four carbonyl signals at δ 158·73, 160·60, 170·33, and 192·25, respectively. The compound present in next larger amount is identified as 7α-spiroepoxide *IIa* (R_1 = R = isopropyl) on the basis of its ^{1}H NMR spectrum (Table I). The component present in smallest amount is identified as a non β-lactam ring enlarged product *V*(R = isopropyl) on the basis of its ^{1}H NMR spectrum which shows a doublet at δ 8·26 (J = 7·0 Hz, collapsed to a singlet on D_2O exchange) and a broad doublet at δ 7·28 (exchangeable with D_2O). From the benzaldehyde reaction ring enlarged product *V*(R = Ph) was also isolated. Similar ring enlarged product was obtained in the $BF_3.Et_2O$ catalyzed reaction of 6-diazopenicillanate with acetaldehyde[9].

TABLE I

Physical and spectral data of 7α-spiroepoxide cephalosporanate 1,1-dioxides (*IIa*)

Compound	Formula (M.w.)	M.p., °C	IR, cm^{-1}	^1H NMR
IIa $R_1 = CH_3$	$C_{16}H_{21}NO_8S$ (387·4)	194–195 (decomp.)	1 781, 1 724, 1 632	1·56 s, 9 H; 1·60 d, 3 H (J = 5·2); 2·10 s, 3 H; 3·73 d, 1 H (J = 18·5); 4·0 d, 1 H (J = 18·3); 3·79 q, 1 H (J = 5·2); 4·72 d, 1 H (J = 13·5); 5·07 d, 1 H (J = 13·7); 4·94 d, 1 H (J = 1·2)
IIa $R_1 = Ph$	$C_{21}H_{23}NO_8S$ (449·5)	155–157	1 787, 1 721, 1 633	1·57 s, 9 H; 2·09 s, 3 H; 3·75 d, 1 H (J = 18·4); 3·99 d, 1 H (J = 18·5); 4·72 d, 1 H (J = 13·5): 5·12 d, 1 H (J = 13·6); 4·72 bs, 1 H; 5·01 br d, 1 H; 7·31–7·42 m, 5 H
IIa R_1 = 3-thienyl	$C_{19}H_{21}NO_8S_2$ (455·5)	143–145	1 787, 1 717, 1 634	1·56 s, 9 H; 2·09 s, 3 H; 3·75 d, 1 H (J = 18·3); 4·0 d, 1 H (J = 18·3); 4·72 d, 1 H (J = 13·6); 5·12 d, 1 H (J = 13·6); 4·72 d, 1 H (J = 1·2); 5·05 d, 1 H (J = 1·9); 7·04–7·07 m, 1 H; 7·33 bs 1 H; 7·38–7·42 m, 1 H
IIa R_1 = 2-thienyl	$C_{19}H_{21}NO_8S_2$ (455·5)	162–164	1 790, 1 726, 1 633	1·57 s, 9 H; 2·10 s, 3 H; 3·76 d, 1 H (J = 18·3); 4·0 d, 1 H (J = 18·3, J = 13·6); 5·14 d, 1 H (J = 13·7); 4·76 d, 1 H (J = 1·7); 5·23 d, 1 H (J = 1·9); 7·0–7·10 m, 2 H; 7·348 d, 1 H (J = 5·1)

4.4.6 *Tetracyclic Condensed Aromatic Compounds*

4.4.6.1 11*H*-Benzo[*a*]fluorenes

Compounds having this skeleton were prepared as analogues of the estrogenic hormone equilenine. Ethyl 1-methyl-2-oxocyclohexane-1-carboxylate was reacted with 2-naphthylmagnesium bromide, the obtained mixture of stereoisomeric alcohols was dehydrated, the double bond was saturated by catalytic hydrogenation (Pd), the ester function was hydrolyzed and the resulting 1-methyl-2-(2-naphthyl)cyclohexane-1-carboxylic acid was cyclized in the form of the acid chloride with stannic chloride to **393** (ref.[95]). Similar synthesis using 6-methoxy-2-naphthylmagnesium bromide and leaving the double bond untouched[111] led to the crystalline ramic 11-oxo-14,15-dehydro-C-nor-D-homoequilenine methyl ether (**394**).

4.4.6.2 Direction to Hydrocyclopenta[*e*]phenanthrenes

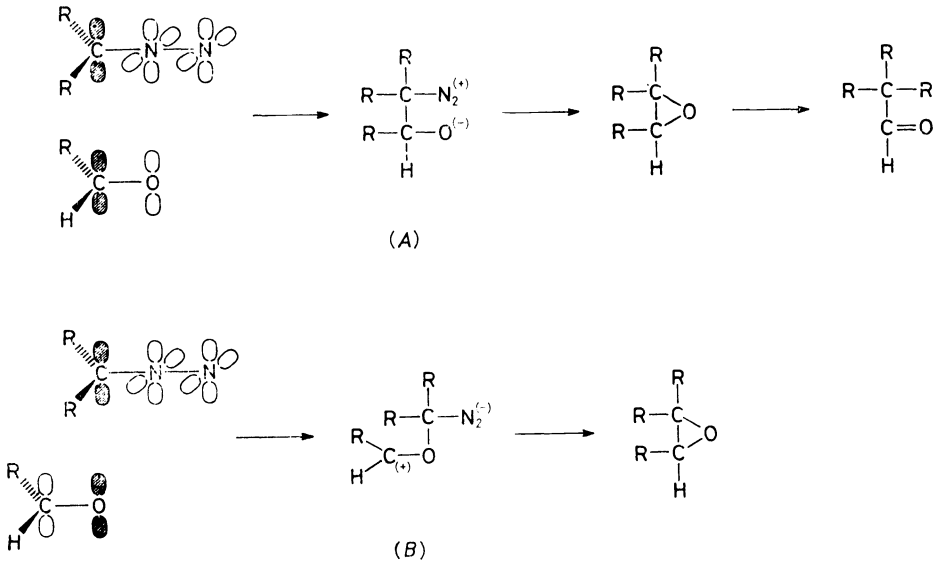
Studies summarized in this paragraph are not classified according to the structure of the products prepared but according to the final goal of the work. Contributions to the total synthesis of the estrogenic hormones were the object of the studies (cf. also refs[6,72,152]). The main contribution consisted in the synthesis of the stereochemically homogeneous esters **395** (ref.[69]) and **396** (ref.[101]). Ethyl 3-(ethoxycarbonylmethyl)-1-methyl-2-oxo-3(4)-cyclohexene-1-carboxylate[69] was subjected to reaction with anisole and aluminium chloride according to the Indian authors[863-865] and **395** was obtained which was transformed by ester exchange to **396**. While refs[863-865] described **395** and **396** only as amorphous mixtures of stereoisomers, our products were crystalline and the dimethyl ester **396** was proven to be identical with an intermediate of an accomplished total synthesis of estrone[866] but obtained by a completely different way. Partial hydrolysis of **395** gave **397**, transformed in crude state to the acid chloride and cyclized with stannic chloride to an inhomogeneous and oily product assumed to be **398** (mixture of stereoisomers) (ref.[101]). Model synthetic experiments[157,174,177] proceeding via **399** – **401** were discontinued because of unsuccessful attempts to C-alkylate these compounds to the desired position (the reason was probably the complete enolization of these compounds).

In an attempt to prepare starting materials for the synthesis of equilenine, 6-acetylnerolin and 6-(3-(methoxycarbonyl)propionyl)nerolin were brominated and structures **402** and **403** were assigned to the products[112]. Dr J. Jacques (College de France, Paris) expressed doubts on the correctness of these structures[867]; in a common work[163], structures **404** and **405** were proven for our products and different methods leading to **402** and **403** were elaborated (bromination with phenyltrimethylammonium perbromide or with pyridinium bromide perbromide). Hydrindan-1,4-dione (**406**) was the object of our attention as a possible CD fragment of the molecules of estrogens. The first synthetic attempt[91] starting from dimethyl 3-nitrophthalate was discontinued after four

VII a b c

SCHEME 2

mediate should collapse leading to the epoxide as the sole product. The mechanism illustrated in Scheme 3 provides a satisfactory explanation for some of the results that have been obtained.



(A)

(B)

SCHEME 3

The interaction of the diazoalkane with carbonyl group is believed to involve a nucleophilic attack on the carbonyl carbon atom i.e., the resonance structure '*a*' contributes more. During the formation of the new C—C bond the carbonyl compound and the diazoalkane are oriented in such a way that the π-bond systems of both the carbonyl group and the diazoalkane moiety overlap in a coplanar fashion (Scheme 3). It is assumed that the reaction takes place in a concerted fashion, i.e., the nitrogen is expelled by backside displacement of the participating group (carbon in the case of aldehyde product, oxygen in the case of epoxide product). It has been reported in the literature that carbonyl compounds containing electron withdrawing

groups tend to give low ketone-to-epoxide ratios[17]. Thus, benzaldehyde, 2-thiophene carboxaldehyde, 3-thiophene carboxaldehyde, 2-furan carboxaldehyde and 3-furan carboxaldehyde form the epoxide as the predominant reaction product while the isobutyraldehyde forms the 7-formyl as the major product. This is interpreted in terms of a reduced migratory aptitude of the R groups of the carbonyl component (i.e., R migrates as a nucleophilic entity) which, thereby, allows the displacement of nitrogen by oxygen (to form epoxide) to take precedence.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. NMR spectra were recorded with a Bruker AC-200E spectrophotometer in $CDCl_3$ and are reported in δ ppm relative to tetramethylsilane as an internal standard. IR spectra were recorded in KBr pellets on a Shimadzu IR-460 spectrophotometer. Microanalyses were performed by Department of Chemistry, University of Alberta.

Tert-butyl 7-Diazo-3-acetoxymethyl-3-cephem-4-carboxylate 1,1-Dioxide[15] (*I*)

Tert-butyl 7-amino-3-acetoxymethyl-3-cephem-4-carboxylate 1,1-dioxide (18·01 g, 0·05 mol) was suspended in 300 ml of chloroform, cooled in an ice-bath, 400 ml of 1·25M-H_2SO_4 was added slowly keeping the temperature between 5—10°C. To this mixture 5·37 g of sodium nitrite dissolved in 75 ml of water was added dropwise maintaining the temperature of the reaction mixture approximately at 5°C, stirred at this temperature for 2·5 h using overhead stirrer. Organic layer was separated, the aqueous layer was re-extracted with chloroform (3 × 80 ml). The organic layers were combined, washed with cold water, sodium bicarbonate solution, brine, dried and concentrated to give a light yellow foam (18·0 g, 96·0%).

Reaction of *I* with 2-Thiophene Carboxaldehyde

To an ice-cooled solution of 7-diazocephalosporanate 1,1-dioxide (*I*, 1·0 g, 2·69 mmol) and 2-thiophene carboxaldehyde (603 mg, 5·38 mmol) in a mixture of methylene chloride–ether (5 ml : 5 ml) was added boron trifluoride etherate (3 drops); a brisk evolution of nitrogen was observed and the mixture was stirred for 5 min. After this an additional drop of boron trifluoride etherate was added, but no evolution of nitrogen was observed and the mixture was stirred for an additional 5 min. The reaction mixture was evaporated to dryness to give a purple foam (1·63 g) which was purified over a silica gel column using ethyl acetate–hexane (2 : 3) followed by preparative TLC (precoated silica plate, 1 mm thickness). The first component *IIa* (R_1 = R = = 2-thienyl) was isolated as a solid (157 mg). Repeated crystallization from ethyl acetate–ether–hexane mixture gave a crystalline solid, m.p. 162—164°C. For ^{1}H NMR see Table I. For $C_{19}H_{21}NO_8S_2$ (455·5) calculated: 50·09% C, 4·65% H, 3·07% N; found: 50·28% C, 4·98% H, 3·34% N.

The second component (*IIIa*) was obtained as a gummy oil, 36 mg. ^{1}H NMR ($CDCl_3$): δ 1·58 s, 9 H; 2·07 s, 3 H; 3·57 d, 1 H (J = 18·4); 3·92 d, 1 H (J = 18·2); 4·69 d, 1 H (J = 13·7); 5·09 d, 1 H (J = 13·7); 4·98 d, 1 H (J = 5·4); 5·33 d, 1 H (J = 5·4); 6·99—7·03 m, 1 H; 7·25—7·34 m, 2 H.

Reaction of *I* with Isobutyraldehyde

To an ice-cooled solution of 7-diazocephalosporanate 1,1-dioxide *I* (1·0 g, 2·69 mmol) and isobutyraldehyde (388 mg, 5·38 mmol) in dry methylene chloride (10 ml) was added one drop of boron trifluoride etherate, brisk evolution of nitrogen was noticed and the mixture was stirred at ice-temperature for 10 min, evaporated to dryness to give a crude mass (1·17 g) which was purified over a silica column followed by preparative TLC. The least polar component was the 7α-spiroepoxide *IIa* (R_1 = R = isopropyl, 12 mg). For ^{1}H NMR see Table I.

The second component (110 mg) was tert-butyl 7-formyl-7-isopropyl-3-acetoxymethyl cephalosporanate 1,1-dioxide (*IV*, R = isopropyl). Repeated crystallization from ethyl acetate–ether–hexane gave a crystalline solid (77 mg, m.p. 165–167°C). ^{1}H NMR ($CDCl_3$): 1·19 d, 6 H (J = 6·8); 1·55 s, 9 H; 2·10 s, 3 H; 2·56 septet, 1 H (J = 6·8); 3·86 ABq, 2 H (J = 18·4); 4·66 s, 1 H; 4·72 d, 1 H (J = 14·0); 5·14 d, 1 H (J = 14·0); 9·93 s, 1 H. For $C_{18}H_{25}NO_8S$ (415·5) calculated: 52·04% C, 6·06% H, 3·37% N; found: 52·15% C, 6·17% H, 3·28% N.

The most polar component was the non β-lactam product *V* (R = isopropyl, 8 mg); crystallization from ethyl acetate–ether–hexane gave a needle like crystal (4 mg, m.p. 144–145°C); ^{1}H NMR ($CDCl_3$): δ 1·11 dd, 6 H (J = 7·0); 1·56 s, 9 H; 1·95 s, 3 H; 3·54 d, 1 H (J = 12·0); 3·77 septet, 1 H (J = 7·0); 4·05 d, 1 H (J = 12·0); 4·36 s, 2 H; 7·28 br d, 1 H (NH, exchanged with D_2O); 8·26 d, 1 H (J = 7·0, collapsed to a singlet on D_2O exchange).

Reaction of *I* with Acetaldehyde

A solution of tert-butyl 7-diazo-3-acetoxymethyl-3-cephem-4-carboxylate 1,1-dioxide (200 mg, 0·5386 mmol) in dry methylene chloride (2 ml) was cooled in an ice-bath, distilled acetaldehyde (0·06 ml, 1·077 mmol) was added followed by two drops of boron trifluoride etherate. The reaction mixture was stirred at 0°C for 15 min, solvent was removed under reduced pressure and the crude product was directly purified over silica column using hexane–ethyl acetate mixture. Elution of the column with hexane–ethyl acetate (2 : 1) gave the desired 7α-spiroepoxide *IIa* (R_1 = R = CH_3, 28 mg) which was crystallized from methylene chloride–ether as white solid (14 mg, m.p. 194–195°C, decomp.). For ^{1}H NMR see Table I. For $C_{16}H_{21}NO_8S$ (387·4) calculated: 49·60% C, 5·46% H, 3·62% N; found: 49·06% C, 5·48% H, 3·37% N.

The second component eluted from the column was 7-formyl-7-methyl-3-acetoxymethyl-3-cephem 1,1-dioxide (*IV*, R = CH_3, 10 mg). ^{1}H NMR ($CDCl_3$): 1·55 s, 9 H; 1·75 s, 3 H; 2·09 s, 3 H; 3·75 d, 1 H (J = 18·3); 4·03 d, 1 H (J = 18·3); 4·70 d, 1 H (J = 13·8); 5·12 d, 1 H (J = = 13·8); 4·71 s, 1 H; 9·95 s, 1 H.

Reaction of *I* with 3-Thiophene Carboxaldehyde

A solution of tert-butyl 7-diazo-3-acetoxymethyl-3-cephem-4-carboxylate 1,1-dioxide (1·0 g, 2·69 mmol) in dry methylene chloride (30 ml) was cooled in an ice-bath, 3-thiophene carboxaldehyde (0·618 g, 5·5 mmol) was added followed by boron trifluoride etherate (4 drops). The reaction mixture was stirred at 0°C for 15 min, solvent was removed under reduced pressure and the crude product was purified over silica column using hexane–ethyl acetate mixture.

The first fraction gave 243 mg (19·76%) as a white foam. This product is assumed as one of the isomeric epoxides, either *IIb* (R_1 = H, R_2 = R = 3-thienyl) or *IIIb* (R_1 = H, R_2 = R = = 3-thienyl). ^{1}H NMR ($CDCl_3$): δ 1·57 s, 9 H; 2·11 s, 3 H; 3·76 d, 1 H (J = 18·5); 4·07 d, 1 H (J = 18·5); 4·71 d, 1 H (J = 13·6); 5·09 d, 1 H (J = 13·6); 5·31 d, 1 H (J = 2·0); 5·44 bs, 1 H; 7·37–7·42 m, 1 H; 7·64–7·67 m, 1 H; 8·43–8·45 m, 1 H.

The second fraction gave 257 mg (20·9%) of *IIa* (R_2 = H, R_1 = R = 3-thienyl) as a white solid. Crystallization from methylene chloride–ether gave analytically pure sample, m.p. 143 to 145°C. For ^{1}H NMR see Table I. For $C_{19}H_{21}NO_8S_2$ (455·5) calculated: 50·09% C, 4·65% H, 3·07% N; found: 50·13% C, 4·90% H, 3·04% N.

The third fraction gave 100 mg (8·1%) of *IV* (R = 3-thienyl) as an oil. ^{1}H NMR ($CDCl_3$): δ 1·57 s, 9 H; 2·07 s, 3 H; 3·80 d, 1 H (J = 18·5); 4·02 d, 1 H (J = 18·4); 4·72 d, 1 H (J = 13·88); 5·159 d, 1 H (J = 13·96); 4·89 s, 1 H; 7·15–7·19 m, 1 H; 7·45–7·48 m, 2 H; 9·83 s, 1 H.

The last fraction gave 28 mg (2·3%) of *IIIa* (R_2 = H, R_1 = R = 3-thienyl) as an oil. ^{1}H NMR ($CDCl_3$): δ 1·58 s, 9 H; 2·08 s, 3 H; 3·55 d, 1 H (J = 18·4); 3·91 d, 1 H (J = 18·2); 4·68 d, 1 H (J = 13·7); 4·98 d, 1 H (J = 5·4); 5·10 d, 1 H (J = 13·7); 5·18 d, 1 H (J = 5·5); 7·16–7·50 m, 3 H.

REFERENCES

1. Giddings P. J., John D. I., Thomas E. J.: Tetrahedron Lett. *1978*, 995.
2. Sheehan J. C., Commons T. J.: J. Org. Chem. *43*, 2203 (1978).
3. Sheehan J. C., Lo Y. S., Loliger J., Podewell C. C.: J. Org. Chem. *39*, 1444 (1974).
4. Chan L., Matlin S. A.: Tetrahedron Lett. *1981*, 4025.
5. Campbell M. M., Harcus R. G., Ray S. J.: Tetrahedron Lett. *1979*, 1441.
6. Giddings P. J., John D. I., Thomas E. J., Williams D. J.: J. Chem. Soc., Perkin Trans 1, *1982*, 2757.
7. Sheehan J. C., Commons T. J., Lo Y. S.: J. Org. Chem. *42*, 2224 (1977).
8. Hanlon B., John D. I., Williams D. J.: J. Chem. Soc., Perkin Trans. 1, *1986*, 2213.
9. Sheehan J. C., Chacko E., Lo Y. S., Ponzi D. R., Sato E.: J. Org. Chem. *43*, 4856 (1978).
10. Bycroft B. W., Shute R. E., Begley M. J.: J. Chem. Soc., Chem. Commun. *1988*, 276.
11. Bycroft B. W., Shute R. E., Begley M. J.: J. Chem. Soc., Chem. Commun. *1988*, 274.
12. Doherty J. B., Ashe B. M., Argenbright L. W., Barker P. L., Bonney R. J., Chandler G. O., Dahlgren M. E., Dorn C. P. jr., Finke P. E., Firestone R. A., Fletcher D., Hagmann W. K., Mumford R., O'Grady L., Maycock A. L., Pisano J. M., Shah S. K., Thompson K. R., Zimmerman M.: Nature *322*, 192 (1986).
13. Shah S. K., Brause K. A., Chandler G. O., Finke P. E., Ashe B. M., Weston H., Knight W. B., Maycock A. L., Doherty J. B.: J. Med. Chem. *33*, 2529 (1990) and references therein.
14. Doherty J. B., Ashe B. M., Finke P. E., Shah S. K., Thompson K. R., Zimmerman M. (Merck): U.S. 4, 547, 371.
15. Blacklock T. J., Butcher J. W., Sohar P., Lamanec T. R., Grabowski E. J. J.: J. Org. Chem. *54*, 3907 (1989).
16. Weissenberger A. (Ed.): *Heterocyclic Compounds with Three- and Four-Membered Rings*, part I, p. 158. Wiley, New York 1964.
17. Gutsche C. D.: Org. React. *8*, 364 (1954).