indicates that this carbonyl group is the most reactive one in the molecule. Consequently, hydrazine attacks the isoimide carbonyl forming an addition intermediate. Opening of the imino lactone gives the corresponding hydrazide which in turn cyclizes to a six-membered cyclic intermediate. Finally, after the cleavage of the carbon–nitrogen bond, the desired nucleus, **7**, is formed.

The described dephthaloylation is relatively simple, fast, and high-yielding. No racemization has been observed during the dephthaloylation procedure. Therefore, we hope that the results of this study will expand the usefulness and applicability of the phthaloyl protective group in synthetic work.[14]

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(11) All new compounds in this paper are characterized by elemental analysis and ir and NMR spectra.
(12) In the case of desacetoxycephalosporins **4a**, **4d**, and **4c** the corresponding 7-(2-carboxybenzamido)-3-methyl-2-cephem-4-carboxylic acid was also isolated in 7, 10, and 24% yield, respectively: mp 196–198° dec; ir (KBr) 1773, 1700, and 1658 cm^{-1}; NMR (DMSO-d_6), δ 1.88 (s, 3), 4.64 (s, 1), 5.15 (d, 1, J = 4.0 Hz), 5.5 (dd, 1, J = 4.0 and 8.0 Hz), 6.15 (s, 1) and 7.4–8 (m, 4 arom H).
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Azetidinone Antibiotics. XV. Synthesis of 2,3-Methylenecepham Derivatives via Intramolecular Cyclization of Diazosulfoxides

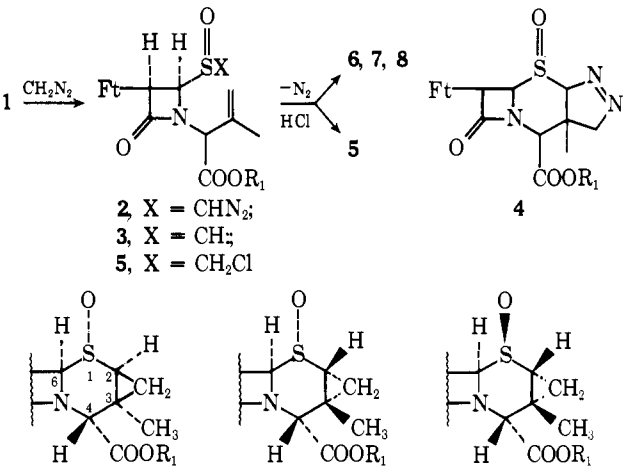
Sir:

The outstanding antibacterial activity of penicillins and cephalosporins has stimulated numerous investigations of chemical modifications of azetidinone antibiotics. Recently, there has been an active interest in the variations of the heterocyclic system attached to the azetidinone ring.[1] The present investigation was initiated to prepare azetidinone containing compounds that contain ring systems other than the thiazolidine or dihydrothiazine found in penicillins and cephalosporins. The proximity of the sulfinyl group in *p*-nitrobenzyl 3-methyl-2-(2-chlorosulfinyl-4-oxo-3-phthalimido-1-azetidinyl)-3-butenoate (**1**)[2] and the olefinic double bond has prompted us to study cyclization of **1** to tricyclic azetidinone derivatives. We postulated that the diazosulfoxide **2** (derived from sulfinyl chloride **1** by reaction with diazomethane) would undergo a cyclization analogous to that observed in olefinic diazoketones.[3,4]

When a solution of **1** was added dropwise to 2.2 equiv of diazomethane (CH_2Cl_2, 0–5°), vigorous nitrogen evolution was noted (2 hr, 5°, and then 2 hr, 25°). The crude mixture was chromatographed to provide four compounds: **5**, mp 177.5–178.5° (27%);[5] **6**, mp 272–273° dec (12%); **7**, mp 236.5–238° dec (20%); and **8**, mp 237–238° dec (2%). The tricyclic ring structure of the title compounds is supported by their NMR spectra (Table I). Quite conspicuous was the disappearance of the olefinic protons and methyl group of the starting sulfinyl chloride **1**, as well as the appearance of a saturated methyl group, the upfield multiplet attributed to the methylene protons of a cyclopropyl group, and a new quartet due to the methine proton at the C-2 position.

The stereochemical assignments of the tricyclic cephams made in regard to the 2,3-methylene substituent are based primarily on NOE measurements. The 2α,3α-methylene and 3β-methyl groups in **7** and **8** exhibit an NOE of 8 and 11%, respectively, indicating a substantial interaction between the vicinal 3-methyl protons and H-4, thus indicating the cis relationship of these substituents. On the other hand, an NOE determination based on the 3-methyl protons and H-4 of compound **6** showed only trace interaction; this is indicative of the 2β,3β-methylene-3α-methyl stereochemistry. Furthermore, irradiation of the 2,3-methylene protons in **6** resulted in enhancement of the H-4 signal, a phenomenon which could be expected considering the spatial proximity of the H-4 and methylene protons in **6**.

The stereochemical assignments of the sulfoxide functionality were made in accordance with the procedure of Cooper et al.[6]



Ft = phthalimido, R_1 = *p*-nitrobenzyl (pNB)

The reaction of **1** with diazomethane to give the proposed intermediate diazosulfoxide **2** probably proceeds in much the same way as a carboxylic acid chloride with diazomethane produces a diazoketone. However, in general, a diazosulfoxide seems to be considerably more reactive than a diazoketone. The diazosulfoxide **2** reacts at low temperature without the use of a catalyst in sharp contrast to the standard thermal copper-catalyzed decomposition of diazoketones.[7]

The formation of products **5**, **6**, **7**, and **8** suggest two, or

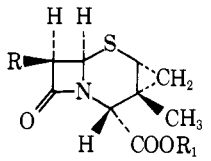
Table I. Spectral Data of 2,3-Methylenecephams[a]

Compound[c]	Solvent	3-CH_3	2-H[e]	4-H	6-H[d]	7-H[d]	Ir(cm^{-1})[b]
6	TFA	79	173 (6, 9.5)	310	320 (4.2)	361 (4.2)	1782
7	$CDCl_3$	95	165 (6.5, 8.5)	288	268 (4.0)	362 (4.0)	1785
8	TFA	101	174 (6, 9)	323	303 (3.8)	367 (3.8)	1785
9	$CDCl_3$	94	111 (5.5, 9.5)	304	305.5 (4.0)	338.5 (4.0)	1788
10	$CDCl_3$	88	114 (5.5, 8.0)	294	317 (4.0)	330 (4.0)	1788
11	$CDCl_3$	94	112 (6.0, 7.5)	298	301 (4.0)	338 (4.0)	1785
12	$CDCl_3$	85	114 (5.5, 8.0)	291	318 (4.0)	333 (4.0)	1790
16	$CDCl_3$	81	109 (5.0, 8.0)	277	290 (4.0)	335[e] (4.0, 8.5)	1780
17	$CDCl_3$	69	110 (5.5, 7.5)	303 (4.0)		321[e] (4.0, 8.0)	1787

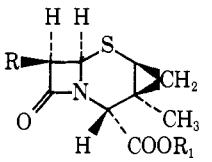
[a] NMR chemical shifts measured in Hz from TMS on a Varian HA-60 instrument, J (Hz) in parentheses. [b] Azetidinone C=O. [c] Satisfactory analyses were obtained for all new compounds. [d] Doublet. [e] Quartet.

possibly three, competing reactions of **2**. First is the reaction of **2** with HCl to give the chloromethylsulfoxide **5**, the major reaction product. Products **6**, **7**, and **8** arise from the diazosulfoxide intermediate by one or both of two possible routes; that is, via the sulfoxo carbene intermediate **3** or the pyrazoline **4**.

Inasmuch as our ultimate goal was to prepare tricyclic azetidinones for biological testing, the sulfoxides were reduced to the corresponding sulfides, and subsequently, the carboxyl protective group was removed. Thus, **6** and **8** were reduced with 1 equiv of phosphorus tribromide in dimethylformamide to the corresponding 2α,3α-methylenecepham (**9**) (22°, 20 min, 90%). Likewise, compound **7** was reduced to provide the corresponding 2β,3β-methylene (**10**) (94%).



9, R = Ft, R_1 = pNB;
11, R = Ft, R_1 = H;
15, R = NH_2, R_1 = H;
17, R = $PhCH_2CONH$, R_1 = H

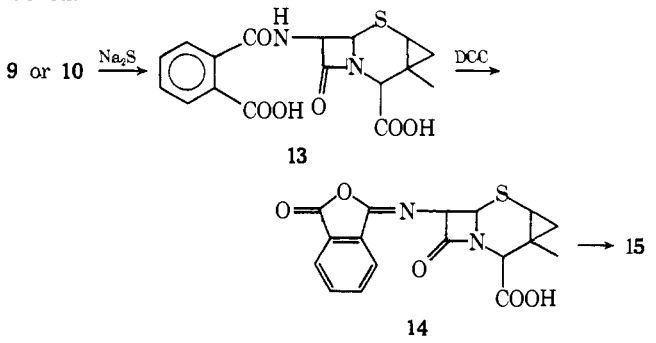


10, R = Ft, R_1 = pNB;
12, R = Ft, R_1 = H;
15, R = NH_2, R_1 = H;
16, R = $PhCH_2CONH$, R_1 = H

The *p*-nitrobenzyl group was removed by catalytic hydrogenation (Pd/C, THF-ethanol) from compounds **9** and **10** to give acids **11** and **12**. Compounds **11** and **12** exhibited no antibacterial activity as determined by a standard disk assay test.

Removal of the phthaloyl group was accomplished in accordance with the general procedures discussed earlier.[8] Scheme I illustrates the three-step sequence for conversion of **9** and **10** to their respective isomeric amino acids (**15**).

Scheme I



13

14

Hydrolysis of the phthalimido protected tricyclic cepham ester (2 equiv of $Na_2S \cdot 9H_2O$, aqueous THF, 0°) gives the diacid **13** (>95%).[9] Treatment of **13** with 1 equiv of dicyclohexylcarbodiimide (THF, 25°) provides the phthalisoimido derivative **14** which is treated with 2 equiv of methylhydrazine (THF, −70°) to give the water soluble amino acid **15**. Both isomers (α- and β-methylene) of **15** were prepared by this route from their respective *p*-nitrobenzyl esters.

A Schotten-Baumann acylation of the isomers of **15** with phenylacetyl chloride gives the desired phenylacetamido compounds **16** and **17** (>50% yield) based on the diacid **13**. In a standard disk assay test both **16** and **17** at 2 mg/ml exhibited activity against: *Staphylococcus aureus*, *Bacillus subtilis*, *Sarcina lutea*, *Proteus vulgari*, and *Escherichi coli*. Of the two compounds, **16** consistently showed slightly better activity.

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(9) Hydrolysis of the *p*-nitrobenzyl ester group under these conditions has been found to be generally applicable.

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Tetrafluorocyclobutadiene

Sir:

The simplest perfluoroannulene occupies a place of special interest, particularly in light of the striking contrasts which set fluorocarbons apart from their hydrocarbon analogs.[1] We wish to report a synthesis of the short-lived tetrafluorocyclobutadiene,[2,3] whose intermediacy is revealed by its transformation and trapping products.

Hexafluoro(Dewar benzene), prepared by vapor-phase