slowly, typically less than 5 mV/min. This is consistent with the slow rate of reaction 7.

The steady-state short-circuit current (lamp on) ranged from 20 to 70 μA, depending on the $[Ru(bpy)_3]^{2+}$ concentration. The cell could be recycled repeatedly over a period of days with no deterioration of performance. These figures represent the greatest potentials reported to date for a cell of this type.[3c]

The Hg^{2+}-quenched system represents a unique system in the area of storage of reversible excited-state electron-transfer energy. With no attempt at optimization, at $[H^+] = 0.1$ M the products Hg_2^{2+} and $[Ru(bpy)_3]^{3+}$ will coexist for >20 min, which represents ~5 orders of magnitude improvement over the $[Ru(bpy)_3]^{3+}/Fe^{2+}$ system.[3c] The energy stored in the $[Ru(bpy)_3]^{3+}/Hg_2^{2+}$ couple is ~7.7 kcal/mol of $[Ru(bpy)_3]^{3+}$, which could represent a maximum ~15% efficient utilization of the 51 kcal zero-point excited-state energy of $*[Ru(bpy)_3]^{2+}$.[9] This calculation assumes no losses through reaction 5. For transition-metal photosensitizers with CT excited states, the available evidence points to ϕ' being unity,[8] and losses through this pathway do not need to be considered. While the efficiency per photon is not high, the trap system does not absorb the UV–vis component of the solar spectrum which allows considerable flexibility in sensitizer selection. In contrast to organic energy traps (e.g., thionine), the completely inorganic Hg^{2+}/Hg_2^{2+} system should be free of the instabilities of large organic molecules. Chemical modifications of the sensitizer to extend the absorption cutoff wavelength and thus the fraction of the solar spectrum absorbed and modifications of the Hg^{2+}/Hg_2^{2+} couple to improve per photon efficiency are presently under investigation.

Acknowledgment. We gratefully acknowledge the assistance of James Madison University and the National Science Foundation (CHE-77-20379).

B. A. DeGraff*

Department of Chemistry, James Madison University
Harrisonburg, Virginia 22807

J. N. Demas*

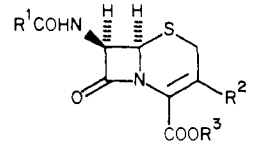
Department of Chemistry, University of Virginia
Charlottesville, Virginia 22901

Received December 17, 1979

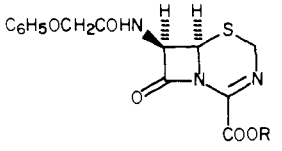
Synthesis of 3-Azacephalosporins

Sir:

The biological activity of the β-lactam antibiotics is generally believed to be associated with the chemical reactivity of their β-lactam rings. For the high reactivity of the β-lactam system in cephalosporins (**1**), a rationalization has been given in terms

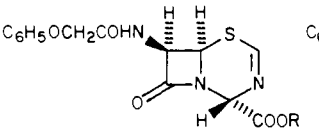


1

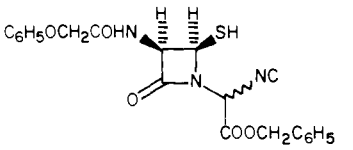


2, R = $CH_2C_6H_5$
20, R = $CH_2OCOC(CH_3)_3$

of an electronic activation by a conjugation of the lone-pair electrons on nitrogen with the C-3 double bond, in competition with the β-lactamamide resonance.[1] We thought that replacement of the C-3 carbon atom of the cephalosporin nucleus with the electron-withdrawing nitrogen atom would enhance the reactivity of the azetidinone carbonyl and consequently modify the antibacterial activity. In this communication, we report a successful approach for preparing this novel bicyclic ring system, 3-azacephem **2**, and the related 3-azacepham nucleus from which the former was derived.



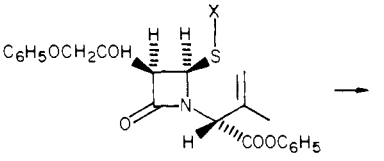
3, R = $CH_2C_6H_5$
21, R = H



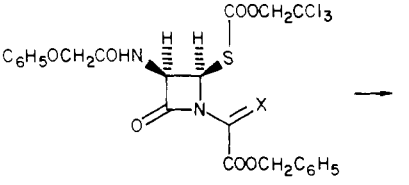
4

Our approach was based on the anticipation that the dihydrothiadiazine ring of **2** could be constructed by a route involving, as a key step, the intramolecular cyclization of the mercapto isocyanide **4** to the Δ^2-azacephem **3**, followed by the conversion of **3** into **2**. Thus, our initial goal was to prepare the isocyanide **4** in which the mercapto group is appropriately protected so as to be readily regenerated by a mild deprotection.

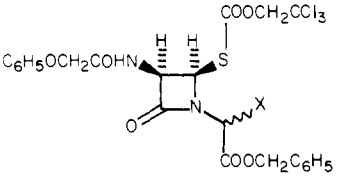
The requisite intermediate, isocyanide **14**, was prepared in a straightforward manner from the 4-mercaptoazetidinone **5**,[2] readily



5, X = H
6, X = $COOCH_2CCl_3$



7, X = $C(CH_3)_2$
8, X = O



9, X = OH
10, X = Cl
11, X = N_3
12, X = NH_2
13, X = NHCHO
14, X = NC

accessible from penicillin V. The mercapto group of **5** was first protected by acylation with (trichloroethoxy)carbonyl chloride (pyridine/CH_2Cl_2), and the product **6** was then treated with Et_3N in benzene, giving the α,β-unsaturated ester **7** (100%). Ozonolysis of **7** (AcOEt, −78 °C), followed by workup with an aqueous solution of $NaHSO_3$ and Na_2SO_3, gave the crystalline oxalyl derivative **8** [mp 152 °C (dec), 77%], which was then subjected to reduction with $NaBH_4$ (AcOH/THF, 0 °C) to give the epimeric alcohol **9** (presumably 1:1). Chlorination of **9** with $SOCl_2$ (2,6-lutidine/CH_2Cl_2, −35 → 0 °C) and subsequent treatment of the resulting chloride **10** with NaN_3 in DMF at 0 °C produced, after purification by silica gel chromatography, the azide **11** [IR (CH_2Cl_2) 2120 cm^{-1}; a ratio of 1:1 on high-pressure liquid chromatography (high-pressure LC)] in 55% yield from **8**. Catalytic reduction of **11** (10% Pd/C, HCO_2H), followed by formylation (HCO_2H/Ac_2O, 0 °C), gave a 77% yield of the formamide **13**, which was finally treated with $POCl_3$ (2,6-

(1) See, e.g.: R. M. Sweet, "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, 1972, pp 305–306.

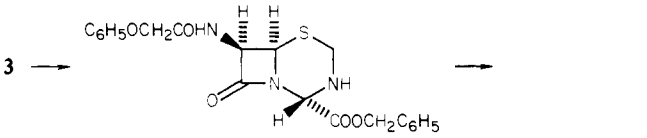
(2) J. E. Baldwin and M. A. Christie, *J. Chem. Soc., Chem. Commun.*, 239 (1978).

0002-7863/80/1502-6171$01.00/0 © 1980 American Chemical Society

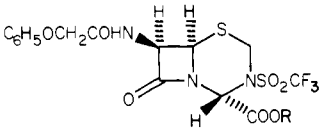
lutidine/CH_2Cl_2, 0 °C) to provide, after chromatographic purification (silica gel), the desired isocyanide **14** [IR (CH_2Cl_2) 2140 cm^{-1}; a ratio of 2:1 on high-pressure LC, 86%].

With the isocyanide **14** in hand, we next focused on the cyclization between the isocyanide and mercapto groups in **14**. For removal of the (trichloroethoxy)carbonyl protective group, **14** was subjected to Zn-dust redution (AcOH/DMF, 0 °C), resulting in the direct formation of the Δ^2-3-azacephem **3** as a single product [mp 141–143 °C, IR (CH_2Cl_2) 1785 cm^{-1}, 48%], which clearly arose via a spontaneous cyclization of the intermediate thiol **4**.[3,4] The structure and stereochemistry of **3** were assigned on the basis of the following ^1H NMR data (in $CDCl_3$). The newly introduced C-2 proton was observed at δ 8.28 with an allylic coupling (d, J = 2 Hz) to the C-4 proton at δ 6.00 (d, J = 2 Hz). The absence of coupling between H-4 and H-7 [δ 5.73 (dd, $J_{6,7}$ = 4 Hz, $J_{7,NH}$ = 9 Hz)] was suggestive of the β configuration of H-4.[5]

The second crucial step was the conversion of **3** into the Δ^3-azacephem **2**. For this purpose, **3** was first reduced by using Al/Hg in aqueous THF at ~5–10 °C to give the 3-azacephem **15** [^1H NMR ($CDCl_3$) δ 4.27 (AB q, J = 14 Hz, 2 H, H-2), 88%].

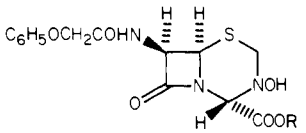


15



17, R = $CH_2C_6H_5$
18, R = H
19, R = $CH_2OCOC(CH_3)_3$

In an attempt to achieve the oxidation with a view toward obtaining **2**, **15** was treated with DDQ (benzene, 50 °C) to furnish the hydroxylamine **16** (mp 184–186 °C; 33%), which was also



16, R = $CH_2C_6H_5$
22, R = H

obtained by oxidation with $CuSO_4 \cdot 5H_2O$ in aqueous AcOH (45%). After further efforts, the conversion of **15** into **2** was eventually achieved as follows. The amine **15** was converted into the triflamide **17** (68%) by acylation with triflic anhydride (2,6-lutidine/CH_2Cl_2, −78 → 0 °C), and **17** was then treated with DBU (CH_2Cl_2, −20 °C) to afford the desired Δ^3-azacephem **2** as an oil in 69% yield after silica gel chromatography. The new cephem was well characterized by its spectral properties [m/e 425.1052 (obsd), 425.1058 (calcd); IR (CH_2Cl_2) 1805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.88 (AB q, J = 9 Hz, 2 H, H-2), 5.10 (d, J = 5.5 Hz, 1 H, H-6), 6.05 (dd, J = 5.5, 10 Hz, 1 H, H-7); UV λ_{max} (THF) 242 nm (ϵ 4500), 332 (500)].

This new cephem nucleus was found to be very unstable,[6] and all attempts to remove the benzyl protective group were unsuccessful.[7] Therefore, we decided to make the pivaloyloxymethyl ester **20** which was expected to be versatile for antimicrobial testing as in the case of penicillins and cephalosporins. The benzyl protective group of **17** was removed by treatment with $AlCl_3$[8] to give the carboxylic acid **18** (96%). Alkylation of **18** with pivaloyloxymethyl iodide (Et_3N/DMF, 0 °C) to the ester **19**, followed by treatment with DBU in a similar manner as described above, yielded **20** in 52% yield. For biological assay, we also prepared the Δ^2-azacephem acid **21** (Na salt) and the hydroxylamine acid **22** from the corresponding esters, **3** and **16**, by hydrolysis with Na_2CO_3 in aqueous THF (100% and 69%, respectively).

The compound **20** was found to show no significant antibacterial activity (≥100 μg/mL) against Gram-positive and Gram-negative bacteria under the test conditions (pH ~6.8–7.0) with or without blood serum. This was probably due to the instability of the Δ^3-3-azacephem nucleus itself. On the other hand, the compounds **21** and **22** were found to be active against *S. aureus* (~25–50 μg/mL), *S. epidermidis* (50 μg/mL), and *E. coli* (100 μg/mL). It was of interest to note that **21** and **22** also showed an MIC value of ~25–50 μg/mL against *Candida albicans* and *Trichophyton asteroides*.

This first synthesis of the 3-azacephalosporins provides a unique opportunity of preparing a structurally and biologically novel type of β-lactam antibiotic, i.e., by acyl exchange of the C-7 amide function in both cephem and cepham series[9] and acylation of the 3-amino function in the cepham series (e.g., **15**).[10]

Acknowledgment. We are indebted to Y. Miyazaki for technical assistance during the course of this work.

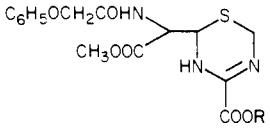
Supplementary Material Available: IR and NMR data for compounds **7–9**, **11**, **14**, **16–18**, and **20** (2 pages). Ordering information is given on any current masthead page.

(3) For reactions of the isocyanides, see, e.g.: U. Schollkopf, *Angew. Chem., Int. Ed. Engl.*, **16**, 339 (1977).

(4) It was presumed that only the *R* isomer, presumably the major one, of the two diastereoisomers **4** cyclized to the cephem **3**. The minor *S* isomer, as shown by an examination with molecular models, seemed to be sterically unfavorable for cyclization and decomposed during the reaction.

(5) (a) D. O. Spry, *Tetrahedron Lett.*, 165 (1973); (b) T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, *J. Am. Chem. Soc.*, **98**, 2343 (1976).

(6) When left in MeOH at room temperature, **2** was almost completely decomposed after 3 h to the non-β-lactam compounds i and ii.

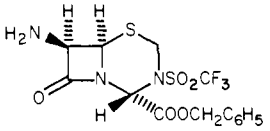


i, R = $CH_2C_6H_5$
ii, R = CH_3

(7) An attempt was also unsuccessful to prepare the carboxylic acid **2** (R = H instead of $CH_2C_6H_5$) by catalytic reduction of the corresponding *p*-nitrobenzyl ester **2** (R = *p*-$CH_2C_6H_4NO_2$ instead of $CH_2C_6H_5$), which was prepared from **18** in a similar manner as for **20**.

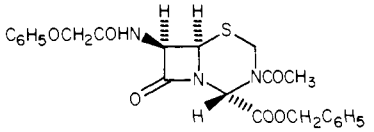
(8) T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda, and W. Nagata, *Tetrahedron Lett.*, 2793 (1979).

(9) Deacylation of, e.g., **17** by the traditional imino chloride procedure gave the amine iii, from which various acyl derivatives could be prepared by reacylation.[11]



iii

(10) E.g., acetylation of **15** with acetyl chloride gave the 3-acetyl-3-azacepham iv.[11]



iv

(11) These minor modifications of the 3-azacephalosporins will be reported in due course.

Matsuhiko Aratani, Masashi Hashimoto*
Research Laboratories
Fujisawa Pharmaceutical Co., Ltd.
Osaka 532, Japan
Received April 24, 1980