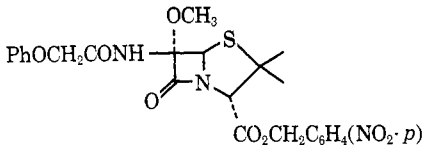
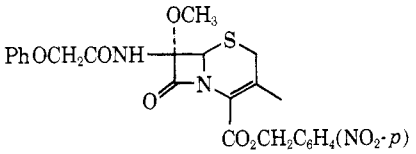


13

vided the deacetoxycephalosporin derivative **14**: nmr



14

($CDCl_3$) δ 8.27 (1, d, J = 8 Hz), 7.60 (1, d, J = 8 Hz), 7.5–6.8 (5, m), 5.28 (2, s), 5.10 (1, s), 4.60 (2, s), 3.57 (3, s), 3.20 (2, s), and 2.57 (3, s). The *p*-nitrobenzyl group of both **13** and **14** was removed by standard procedures[13] to provide the corresponding free acids.

In summary, the method of hypochlorite oxidation of suitable penicillin derivatives allows a direct entry into the 6-α-methoxypenicillins and, by rearrangement, also into the 7-α-methoxydeacetoxycephalosporin compounds.

Acknowledgment. We thank Eli Lilly and Co. for financial support and Dr. W. H. W. Lunn of the Lilly Research Laboratories for many helpful discussions.

(13) D. O. Spry, *Tetrahedron Lett.*, 3717 (1972).
(14) Alfred P. Sloan Fellow, 1969–1971.

J. E. Baldwin,*[14] F. J. Urban
Department of Chemistry, Massachusetts Institute of Technology Cambridge, Massachusetts 02139

R. D. G. Cooper, F. L. Jose
Lilly Research Laboratories, Eli Lilly and Company Indianapolis, Indiana 46206

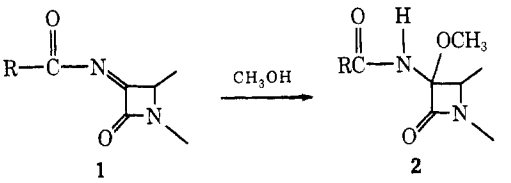
Received December 14, 1972

Functionalization of $C_{6(7)}$ of Penicillins and Cephalosporins. A One-Step Stereoselective Synthesis of 7-α-Methoxycephalosporin C

Sir:

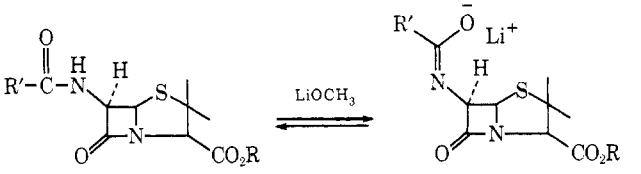
The recent discovery of a new family of 7-methoxycephalosporins has stimulated a synthetic effort to prepare 6-methoxypenicillins and other 7-methoxycephalosporins.[1,2] As was the case with cephalosporin C (**7f**) over a decade ago, it was hoped that the synthetic analogs would have enhanced antimicrobial activity.

Our synthetic objective was to utilize a procedure which would convert a parent penicillin or cephalosporin directly to the $C_{6(7)}$-methoxy derivatives. An attractive intermediate which might lend itself to such a transformation was the acylimine (**1**), for it was anticipated that methanol would add to the strongly electrophilic acylimine to afford the methoxyamide (**2**). Indeed, in a series of experiments, Baldwin and coworkers demonstrated that methanol adds to acylimines derived from α-acetamido acids by a halogenation–dehydrohalogenation sequence using *tert*-butyl hypochlorite to afford the methoxyamides and, more importantly, that the acylimine could be prepared from anhydropenicillin V and that methanol added stereoselectively from the α face.[3] The method is amenable only to penicillins suitably protected as the sulfoxide or sulfone, for it has been well established that the sulfur of penicillin and cephalosporin reacts vigorously with various electrophilic reagents such as *tert*-butyl hypochlorite.[4,5] Furthermore, the C_2 position of cephalosporins is equally reactive to such reagents.[6] These chemical properties of the parent penicillins and cephalosporins prevent them from being functionalized directly by the above procedure.



1 2

An investigation into the possibility of generating penicillin and cephalosporin amide anions by a base such as lithium methoxide previously had not been reported because of the exaggerated myth that β-lactams are unstable to base. Certainly, it can be envisioned that a conjugate base (**3a**) should compete quite favorably for capture of an electrophile. We report here the unexpected stability of penicillins and cephalosporins to lithium methoxide and the resultant application of this discovery to the synthesis of 6-methoxypenicillins and 7-methoxycephalosporins.



3 3a

Treatment of **4a** with 3.5 equiv of lithium methoxide in tetrahydrofuran (THF) at −80° for 1 min followed by quenching with acetic acid afforded a mixture of **4a** and **5a** (9:1).[7,8] When the amide anion, derived from **4a** by the method just described, was treated with 1 equiv of *tert*-butyl hypochlorite followed by stirring for 15 min and quenching with acetic acid, there was obtained after work-up and chromatography, a 70% yield of **4c** as a

(1) (a) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971). (b) E. O. Stapley, D. Hendlin, S. Hernandez, M. Jackson, J. M. Mata, A. K. Miller, H. B. Woodruff, T. W. Miller, G. Albers-Schonberg, B. H. Arison, and J. L. Smith, Abstracts, XIth Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N. J., 1971, p 8.

(2) For other synthetic methods, see L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972); S. Karady, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, *ibid.*, **94**, 1410 (1972); W. A. Spitzer, *et al.*, *Tetrahedron Lett.*, submitted for publication.

(3) J. E. Baldwin, F. Urban, R. D. G. Cooper, and F. L. Jose, *J. Amer. Chem. Soc.*, **95**, 2401 (1973).

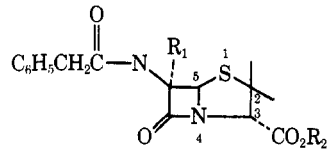
(4) We have found that penicillin G reacts with *tert*-butyl hypochlorite in THF at −80° to afford the sulfoxide.

(5) S. Kukolja, *J. Amer. Chem. Soc.*, **93**, 6267 (1971).

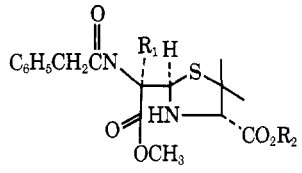
(6) (a) D. O. Spry, *Tetrahedron Lett.*, 3717 (1972). (b) The corresponding cephalosporin sulfoxide affords initially dichlorination on C_2 which then undergoes methoxylation at C_7. R. D. G. Cooper and P. Pranc, Lilly Research Laboratories. (c) If the C_2 position is disubstituted, the corresponding sulfoxide can be methoxylated using the Baldwin procedure, see D. O. Spry, *Tetrahedron Lett.*, submitted for publication.

(7) All new compounds gave good mass spectral or elemental analyses.

(8) (a) The concentration of amide anion has not been determined. (b) Similar treatment of phenoxymethylpenicillin methyl ester afforded starting material without evidence of penicilloate formation.



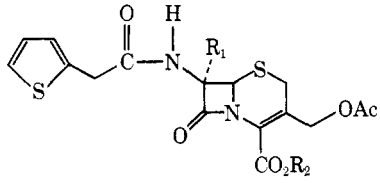
4a, R_1 = H; R_2 = $-CH_2C_6H_4NO_2$
b, R_1 = H; R_2 = H
c, R_1 = OCH_3; R_2 = $-CH_2C_6H_4NO_2$
d, R_1 = OCH_3; R_2 = H



5a, R_1 = H; R_2 = $-CH_2C_6H_4NO_2$

noncrystalline foam:[9,10] ir ($CHCl_3$) 1775, 1745, and 1685 cm^{-1}; nmr τ ($CDCl_3$) H_5 4.41 (s), H_3 5.56 (s), OCH_3 6.60 (s), *gem*-dimethyl 8.70 and 8.50 (s). Hydrogenation of **4c** in methanol–THF using 5% Pd/C gave **4d**.

Having demonstrated the utility of this procedure in the synthesis of 6-methoxypenicillins, we focused our attention on the methoxylation of the cephalosporin molecule. The procedure, by analogy, presented two formidable problems: (1) chlorination at the C_2 position and (2) Δ^3 double bond isomerization.[6] However, treatment of **6a** with lithium methoxide (3.5

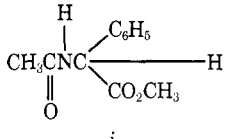


6a, R_1 = H; R_2 = $-CH_2C_6H_4NO_2$
b, R_1 = H; R_2 = H
c, R_1 = OCH_3; R_2 = $-CH_2C_6H_4NO_2$
d, R_1 = OCH_3; R_2 = H
e, R_1 = OCH_3; R_2 = Na^+

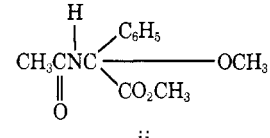
equiv) and *tert*-butyl hypochlorite at −80° followed by work-up and chromatography gave a 73% yield of **6c**:[11] ir ($CHCl_3$) 1780, 1740, and 1695 cm^{-1}; nmr τ ($CDCl_3$) H 4.93 (s), side-chain methylene 6.09 (s), OCH_3 6.54 (s). The acid (**6d**) was obtained *via* hydrogenation in methanol–THF on 5% Pd/C and converted to its sodium salt **6e** (mp 148–150°).

(9) Compound **4c** appears to be more stable to methoxide than the starting penicillin, for treatment of **4b** with 2.5 equiv of lithium methoxide for 15 min afforded a 50% yield of **5a**.

(10) Dr. E. L. Smithwick of Lilly Research Laboratories has demonstrated that under the same conditions, *N*-acetyl-2-phenylglycine methyl ester (i) afforded a quantitative yield of starting material and that, at −20°, one obtained a near quantitative yield of the methoxy amide (ii). These data indicate a reversible O- or N-chlorination followed



i

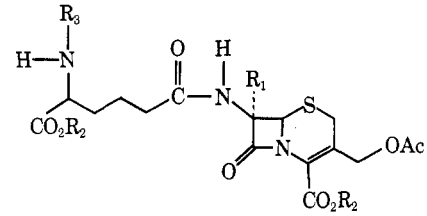


ii

by dehydrohalogenation. Since the α hydrogen of i is less activated than the C_6 hydrogen of penicillin, a higher temperature is required for its proton removal.

(11) There was no evidence of double bond isomerization during the reaction.

It was now apparent that we could confirm the structure of 7-α-methoxycephalosporin C (**7e**) obtained



7a, R_1 = H; R_2 = benzhydryl; R_3 = *tert*-butyloxycarbonyl
b, R_1 = H; R_2 = CH_3; R_3 = *tert*-butyloxycarbonyl
c, R_1 = OCH_3; R_2 = CH_3; R_3 = *tert*-butyloxycarbonyl
d, R_1 = OCH_3; R_2 = benzhydryl; R_3 = *tert*-butyloxycarbonyl
e, R_1 = OCH_3; R_2 = H; R_3 = H
f, R_1 = H; R_2 = H; R_3 = H

by fermentation. Methoxylation of **7b** by the previously described method afforded a 70% yield of **7c**:[12] ir ($CHCl_3$) 1780, 1740, and 1705 cm^{-1}; nmr τ (DMSO-d_6) H_6 4.83 (s), OCH_3 6.62 (s), *tert*-butyl 8.63 (s). The synthesis of **7e** was completed by methoxylating **7a**, utilizing the above described conditions, in 65% yield and removing the protecting groups with trifluoroacetic acid–formic acid to give 7-α-methoxycephalosporin C in 40% yield.[13,14]

Acknowledgment. The author is grateful to Dr. R. Nagarajan for kindly supplying us with the natural derivative and would also like to thank Dr. W. H. W. Lunn for useful discussions during this investigation.

(12) All spectral data were identical with that of the natural derivative.

(13) The spectral and biological assay data were identical with those of the natural derivative.

(14) For an alternate synthesis of **7e**, see R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 2910 (1972).

G. A. Koppel,* R. E. Koehler
The Lilly Research Laboratories, Eli Lilly and Company
Indianapolis, Indiana 46206
Received December 14, 1972

Resonance Energies of Aromatic Hydrocarbons. A Quantitative Test of Resonance Theory

Sir:

Molecular orbital (MO) theory has largely supplanted valence bond (VB) theory for quantitative correlations of stability and reactivity. One important reason is the large number of paired electron structures that comprise canonical sets.[1] For example, 429 nonionic structures can be drawn for the π-electronic system of the relatively small aromatic molecule anthracene. A restriction of VB theory to the simplest structures, *e.g.*, Kekule[2] and Dewar structures, has often been declared to be too inaccurate an assumption for quantitative comparisons.[3]

The crudest variant of VB theory is called resonance theory, in which relative stabilities of isomeric π-molecular species are deduced from enumeration of Kekule structures alone. This crude but highly

(1) L. Pauling, *J. Chem. Phys.*, 1, 280 (1933); J. H. Van Fleck and A. Sherman, *Rev. Mod. Phys.*, 7, 167 (1935).

(2) The words "Kekule structure" will refer to any valence bond structure in which single and double bonds alternate.

(3) A. Pullman, *Ann. Chim. (Paris)*, 2, 5 (1947); P. Daudel and R. Daudel, *J. Chem. Phys.*, 16, 639 (1948); D. P. Craig, *Proc. Roy. Soc., Ser. A*, 200, 272, 390, 401 (1950); C. A. Coulson, *ibid.*, 207, 91 (1951).