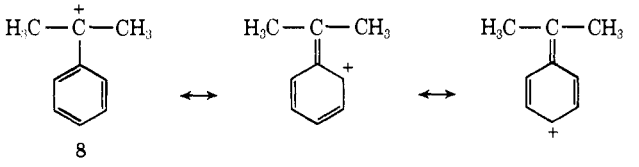
The rate constants and related data are summarized in Table I.

Table I. Rate Data for the Solvolysis of Tertiary 2-Propyl *p*-Nitrobenzoates, $R(CH_3)_2COPNB$, in 80% Acetone

R	$k_1^{25°} \times 10^6$, sec^{-1}	Rel rate, 25°	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
Methyl[a]	7.45×10^{-5} [e]	1.00	29.2	−7.1
tert-Butyl[b]	3.25×10^{-4} [e,f]	4.36	29.0	−4.8
Phenyl[c]	7.22×10^{-2} [e,g]	969	24.8	−8.2
Cyclopropyl[d]	37.5[d,h]	503,000	20.8	−9.0

[a] H. C. Brown and W. C. Dickason, *J. Amer. Chem. Soc.*, **91**, 1226 (1969). [b] Mp 139.8–140.2°. [c] L. F. King, *J. Amer. Chem. Soc.*, **61**, 2383 (1939). [d] M. Hanack and K. Goerber, *Chem. Ber.*, **96**, 2121 (1963). The product of solvolysis is unrearranged cyclopropyldimethylcarbinol: C. D. Poulter and S. Winstein, *J. Amer. Chem. Soc.*, **91**, 3650 (1969). [e] Calculated from data at other temperatures. [f] $k_1^{150°} = 814 \times 10^{-6}$ sec^{-1}; $k_1^{125°} = 89.6 \times 10^{-6}$ sec^{-1}. [g] $k_1^{75°} = 33.6 \times 10^{-6}$ sec^{-1}; $k_1^{100°} = 391 \times 10^{-6}$ sec^{-1}. [h] $k_1^{50°} = 614 \times 10^{-6}$ sec^{-1}.

Since differences in the ground-state energies are not significant in the *tert*-butyl and *tert*-cumyl derivatives, the factor of 10^3 in rates indicates that the transition state of the *tert*-cumyl derivative is stabilized by approximately 4 kcal/mol. The stabilization of the free ion is presumed to be modestly larger.[7] This stabilization is presumed to be due to charge delocalization from the carbonium center into the aromatic ring **8**.



8

Indeed, the large rate enhancement effects of methyl[9a] (×26) and methoxy[9b] (×3360) substituents in the para position support this interpretation.

Similarly, the large rate enhancing effect of the cyclopropyl group ($10^{5.5}$) indicates that the transition state is stabilized by approximately 7.5 kcal/mol. This stabilization must also be the result of major charge delocalization from the carbonium center into the cyclopropane ring. Indeed, here also large rate enhancing effects, following σ^+, have been observed for methyl (×11) and ethoxy (×940) substituents in the cyclopropyl ring.[10]

The major increase in rate observed for the cyclopropyl derivative **6**, as compared to the phenyl derivative **5**, indicates that more charge must be delocalized from the carbonium carbon in **6**, as compared to **5**. If the ^{13}C shifts measure the electron densities on the individual carbon atoms, one would have anticipated a larger ^{13}C shift for the carbonium carbon in the ion from **6** as compared to that from **5**. The fact that the magnitude of the ^{13}C shift occurs in the opposite direction led Olah and his coworkers to conclude that phenyl is a better electron-releasing group than cyclopropyl, a conclusion directly opposite to that indicated by the present solvolytic study, as well as by other approaches.[6] Clearly it is desirable that we proceed with caution in basing conclusions as to electron densities on carbon atoms on ^{13}C shifts alone until this major discrepancy is resolved.[11]

(9) (a) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Amer. Chem. Soc.*, **79**, 1897 (1957); (b) Y. Okamoto and H. C. Brown, *ibid.*, **79**, 1909 (1957).

(10) P. von R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966). The data are for 100°, rather than the 25° values used otherwise.

(11) Other discrepancies are evident. For example, the rates of solvolysis of 1-methylcyclopentyl (1.00) and 2-methyl-*exo*-norbornyl *p*-nitrobenzoates (4.0) are comparable: H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Amer. Chem. Soc.*, **86**, 1247 (1964). Yet the ^{13}C shifts for the corresponding cations, −142 and −76, are very different: G. A. Olah, A. M. White, J. R. DeMember, A. Commeyras, and C. Y. Lui, *ibid.*, **92**, 4627 (1970).

(12) Graduate research assistant on a grant (GP 31385) supported by the National Science Foundation.

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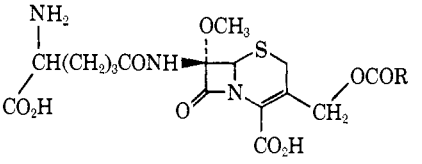
Received October 2, 1972

Direct 6-Methoxylation of Penicillin Derivatives. A Convenient Pathway to Substituted β-Lactam Antibiotics

Sir:

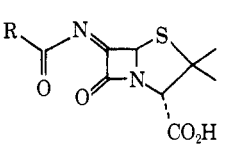
The recent isolation and structure proof of the new β-lactam-containing antibiotics **1a–d** from *Streptomyces*



1a, R = CH_3
b, R = NH_2
c, R = $-C(OCH_3)=CHC_6H_4OH\text{-}p$
d, R = $-C(OCH_3)=CHC_6H_4OSO_3\text{-}p$

have aroused considerable interest, since these materials contained a functionability heretofore unknown in the general group of penicillin and cephalosporin compounds, namely a 7-methoxyl group.[1] The enhanced activity against Gram-negative bacteria of these new antibiotics encouraged us to develop a method for the direct, one-step introduction of a methoxyl substituent at C-6 into the penicillin nucleus. Since a procedure for the conversion of penicillin to the cephalosporin system is now well established,[2] access would thereby be obtained to methoxyl-substituted penicillin and cephalosporin compounds. We report the first direct method for this transformation.[3]

Our approach has been the generation of a reactive



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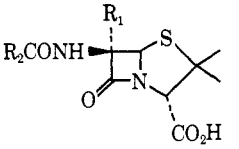


3, $R_1 = OCH_3$

(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, R. 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) R. B. Morin, B. J. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **91**, 1401 (1969).

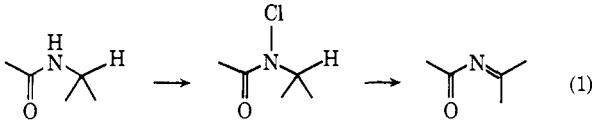
(3) A recent communication describes the partial synthesis of 6-α-methoxyl-substituted penicillins starting from 6-diazo compounds; *cf.* L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972).

intermediate, the acylimine **2**, which would predictably undergo Michael addition of nucleophiles at C-6. In a solvent, such as methanol, addition would be expected to occur from the α and less substituted face to yield 6-α-methoxyamides of type **3**.[4] We have found that the N-chlorination–dehydrochlorination sequence, as represented by eq 1, successfully generated the acylimine.

$$\begin{array}{l} PhC(OCH_3)CO_2CH_3 \\ | \\ NHCHCO_2Ph \end{array}$$

4

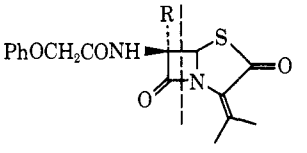
Thus, in a model study, treatment of *N*-(phenylacetyl)-DL-2-phenylglycine methyl ester with *tert*-butyl hypochlorite in methanolic sodium borate solution at 0°[5,6] gave the derivative **4** in 90% yield: mp 126–127°



(1)

(benzene–pentane); ir ($CHCl_3$) 3400, 1720, and 1680 cm^{-1}; nmr ($CDCl_3$) δ 3.15 (3, s), 3.50 (3, s), and 7.25 (11, m). The masked ketone nature of compound **4** was readily exposed by dilute acid hyrolysis to methyl benzoylformate and phenylacetamide.

Anhydropenicillin **5**[7] was similarly oxidized at 0° to a nearly quantitative yield of the 6-methoxyl derivative **6**,

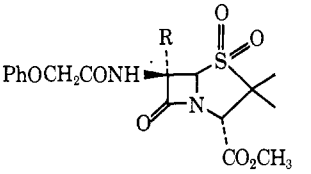


5, R = H

6, R = OCH_3

mp 103–105°. The spectral and analytical data for **6** were in complete accord with the formulation, *i.e.*, ν_{max} 1785 and 1700 cm^{-1}; nmr ($CDCl_3$) δ 7.9 (1, s, NH), 7.5 (5, m, aryl), 5.65 (1, s, C-5), 4.56 (2, s, CH_2), 3.54 (3, s, OCH_3), and 2.17 (3, s, *gem*-CH_3). The mass spectrum of **6** showed no parent ion but had the characteristic fragmentation of the β-lactam moiety of (*cf.* **6**, dotted line) M^+ 141 and 221, this cleavage indicating attachment of the methoxyl group at C-6. Proof of this structure was obtained by an X-ray crystallographic study.[8]

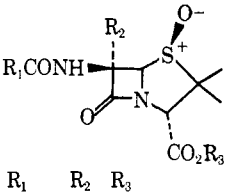
Due to the sensitivity of the thiazolidine sulfur to *tert*-butyl hypochlorite, we have utilized both sulfone and sulfoxide functions as protecting groups. Thus, the sulfone **7**, under the above conditions, gave derivative **8** in 56% isolated yield: ν_{max} 1790 and 1750 cm^{-1}; nmr ($CDCl_3$) δ 7.78 (1, s), 7.5 (5, m), 4.98 (1, s), 4.58 (2, s), 4.41 (1, s), 3.79 (3, s), 3.42 (3, s), 1.5 (3, s), and 1.37 (3, s). The sulfoxide **9a** with *tert*-butyl hypochlorite (3 equiv added over a 2-hr period at 0°) in methanol containing sodium borate buffer gave a 60% yield of the



7, R = H

8, R = OCH_3

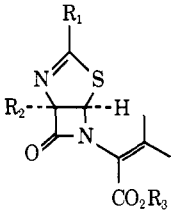
7-methoxyl derivative **10a**, ν_{max} 1790 and 1755 cm^{-1}.



	R_1	R_2	R_3
9a,	$PhOCH_2$	H	CH_3
9b,	$PhOCH_2$	H	$CH_2C_6H_4(NO_2\text{-}p)$

	R_1	R_2	R_3
10a,	$PhOCH_2$	OCH_3	CH_3
10b,	$PhOCH_2$	OCH_3	$CH_2C_6H_4(NO_2\text{-}p)$

The nmr of **10a** and its aromatic induced solvent shifts were suggestive of the 6-α-methoxyl configuration. Final proof of the cis relationship beteen the amide side chain and the C_5 sulfur was obtained by rearrangement of **10b** with trimethyl phosphite[9] when the thiazoline **11** was obtained: ν_{max} 1770 and 1720 cm^{-1}; nmr ($CDCl_3$) δ 8.22 (2, d, J = 9 Hz), 7.51 (2, d, J = 9 Hz), 7.28 (5, s), 5.66 (1, s), 5.25 (2, s), 3.89 (2, s), 3.53 (3, s), 2.20 (3, s), and 1.53 (3, s). Comparison of the ORD curve of **11** with that of thiazoline **12**, prepared from sulfoxide **9b**,



	R_1	R_2	R_3
11,	$PhOCH_2$	OCH_3	$CH_2C_6H_4(NO_2\text{-}p)$
12,	$PhOCH_2$	H	$CH_2C_6H_4(NO_2\text{-}p)$

showed very similar curves execpt that **11** exhibited a small bathochromic shift due to the methoxyl group. The β-sulfoxide configuration of **10a** was substantiated by a ^{13}C nmr spectrum which showed the *gem*-dimethyl resonances at 172.5 and 173.0 ppm in excellent agreement with the previously reported values for **9a**.[10]

Reduction of the sulfoxide **10b** using PBr_3–DMF[11] gave the 6-α-methoxypenicillin ester **13** as an oil: ν_{max} 1780 and 1750 cm^{-1}; nmr ($CDCl_3$) δ 8.27 (1, d, J = 8 Hz), 7.60 (1, d, J = 8 Hz), 7.5–6.8 (5, m), 5.65 (1, s), 5.32 (2, s), 4.60 (2, s), 4.53 (1, s), 3.53 (3, s), 1.47 (3, s), and 1.40 (3, s).

Ring expansion rearrangement of **10b** with dipyridinium phosphate catalyst in refluxing dioxane[12] pro-

(4) Several cases exist which indicate that a C-6 trigonally hybridized system can be intercepted kinetically from the α face; *cf.* G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, *J. Amer. Chem. Soc.*, **93**, 2342 (1971), also ref 3a and 3b.

(5) J. S. Chalstry and S. S. Israelstam, *Chem. Ind. (London)*, 1452 (1954).

(6) All new compounds have given satisfactory spectral and analytical data.

(7) S. Wolfe, J. C. Godfrey, C. T. Haldrege, and Y. G. Perron, *Can. J. Chem.*, 2549 (1968).

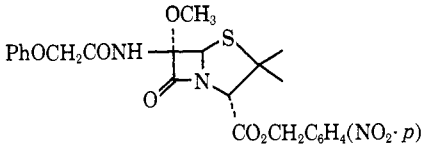
(8) M. O. Chaney and N. D. Jones, Lilly Research Laboratories, personal communication.

(9) R. D. G. Cooper and F. J. Jose, *J. Amer. Chem. Soc.*, **92**, 2575 (1970).

(10) In ppm from the ^{13}C resonance of Me_4Si, *cf.* R. A. Archer, R. D. G. Cooper, and P. V. Demarco, *Chem. Commun.*, 1291 (1970).

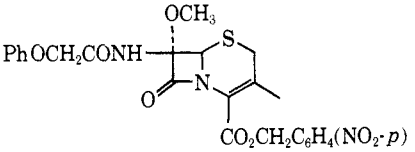
(11) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, **35**, 2430 (1970).

(12) Belgium Patent 747119 (Nov 3, 1969).



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.

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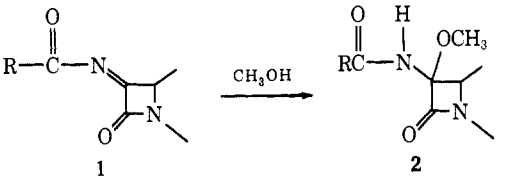
Received December 14, 1972

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

Sir:

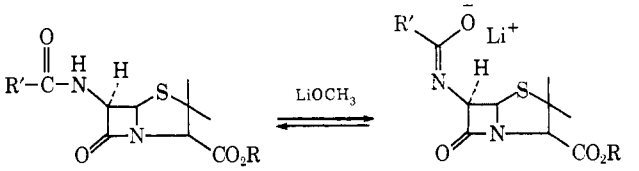
The recent discovery of a new family of 7-methoxycephalosporins has stimulated a synthetic effort to prepare 6-methoxypenicillins and other 7-methoxycephalosporins.[1,2] As was the case with cephalosporin C (**7f**) over a decade ago, it was hoped that the synthetic analogs would have enhanced antimicrobial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