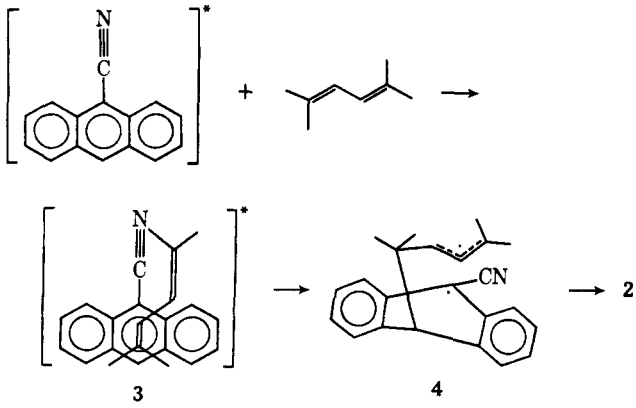

3 4

pentadienes, the structure of the adducts seems to be determined by the stability of the biradical **4** formed. Our results strongly suggest that the reaction pathway of a photochemical addition may be controlled by the configuration of two components in the exciplex intermediate.

The thermal $4_\pi + 2_\pi$ cycloaddition reactions including the Diels–Alder reaction are widely used in the organic synthesis, and this reaction, a $4_\pi + 2_\pi$ stereospecific photocycloaddition, may be complementary to the Diels–Alder reaction in the organic synthesis. The scope and limitation of this reaction are being investigated.

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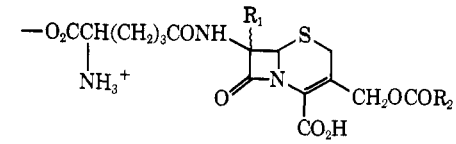
Substituted Penicillin and Cephalosporin Derivatives. I. Stereospecific Introduction of the C-6(7) Methoxy Group

Sir:

It has been suggested that an α-methyl group at C-6 of the penicillin nucleus would enhance antibacterial activity.[1] Several groups have attempted modifications at this position.[2] Recently we have developed synthetic routes to 6-methoxypenicillins and 7-methoxycephalosporins. Our interest in these compounds also arises from the discovery of four members of the cephamycin[3] class (**1a–d**), each of which contains a 7-methoxyl substituent.[4] Like cephalosporin C (**1e**), these new cephalosporins contain an α-aminoadipoyl side chain and its interchange to other acyl side chains was presumed necessary in order to obtain medicinally useful antibacterials.[5] We report here the partial synthesis of such compounds as well as a general method for the stereospecific introduction of a methoxy group adjacent to the β-lactam group in both the penicillin and cephalosporin series.



1a, $R_1 = OCH_3$; $R_2 = NH_2$
b, $R_1 = OCH_3$; $R_2 = CH_3$
c, $R_1 = OCH_3$; $R_2 = -C(OCH_3)=CHC_6H_4OH\text{-}p$
d, $R_1 = OCH_3$; $R_2 = -C(OCH_3)=CHC_6H_4OSO_3^-\text{-}p$
e, $R_1 = H$; $R_2 = CH_3$

Although the reactions of aliphatic diazocarbonyl compounds with halogens and pseudohalogens[6] are well known, their reaction with bromine azide has not been reported. Treatment of benzyl 6-diazopenicillanate[7] with bromine azide and excess triethylammonium azide in methylene chloride at $-15°$ resulted in a mixture of epimeric 6-bromo-6-azidopenicillanates **2a** and **b** (see Scheme I): ir (film) 2120 cm^{-1} (azide). The isomers could be separated by crystallization of **2a** (mp 62–63°) out of the mixture. Both isomers gave the same benzyl 6β-azido-6-methoxypenicillanate (**3a**): mp 60–61°; ir (CH_2Cl_2) 2125, 1785, 1750 cm^{-1}, upon treatment with $AgBF_4$ in methanol at room tempera-

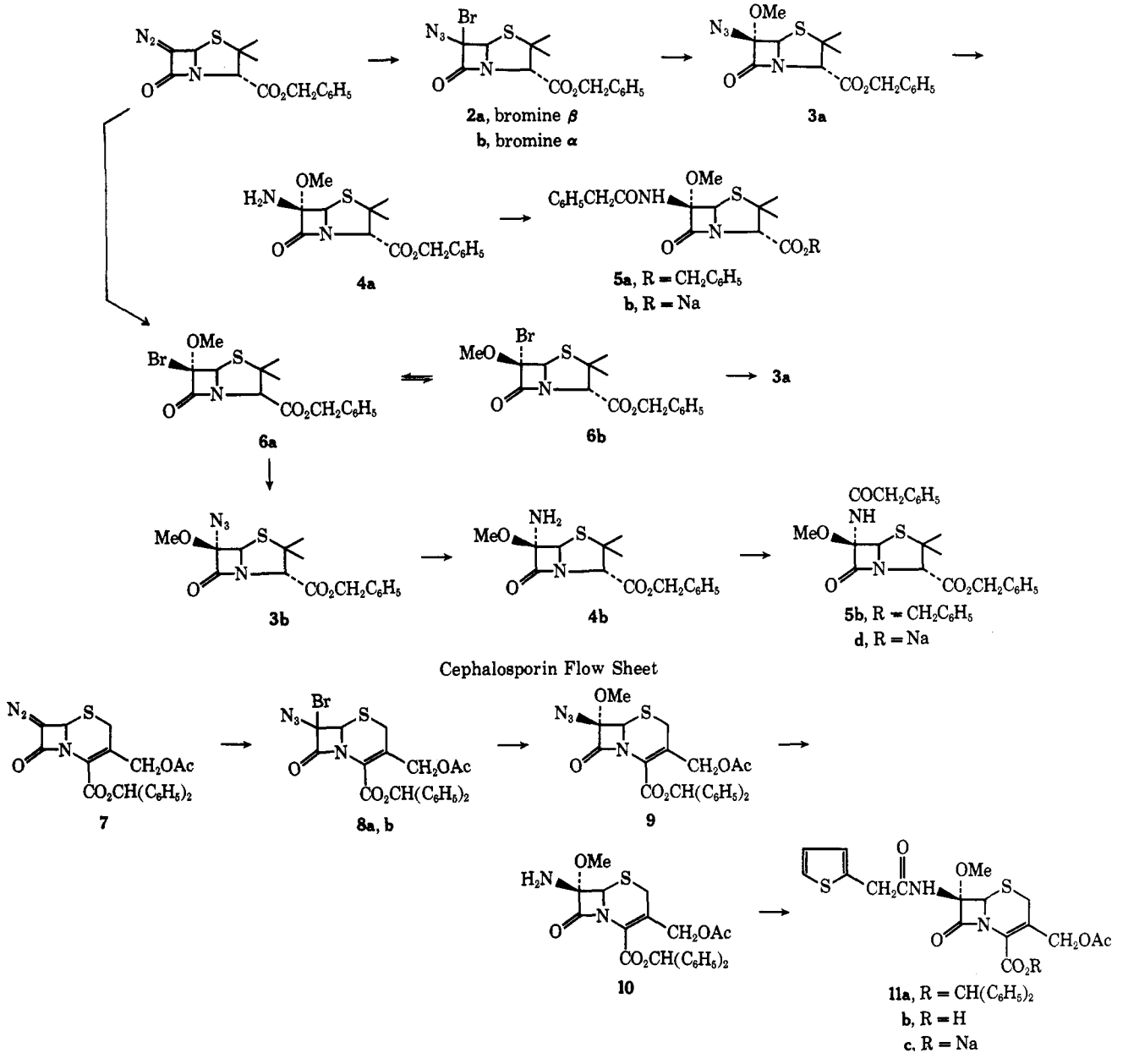
Table I. Nmr Data of Penicillins ($CDCl_3$)

Compd	Chemical shift, τ (TMS) H_5	H_3	2-CH_3	OCH_3
2a	4.68	5.47	8.40, 8.62	
2b	4.29	5.47	8.42, 8.62	
3a	4.61	5.49	8.42, 8.59	6.37
3b	4.75	5.52	8.48, 8.64	6.45
4a	4.63	5.51	8.45, 8.60	6.53
4b	4.80	5.53	8.44, 8.51	6.57
5a	4.40	5.59	*8.70*	6.59
5b	4.32	5.54	8.44, 8.62	6.62
5c[a]	4.49	5.74	8.59, 8.61	6.51
5d[a]	4.53	5.72	8.45, 8.49	6.58
6a	4.55	5.48	8.40, 8.62	6.34
6b	4.26	5.48	8.47, 8.60	6.38
Benzyl 6,6-dibromopenicillanate[b]	4.20	5.44	8.41, 8.62	

[a] D_2O was the solvent used with **5c** and **5d**. [b] Obtained as a by-product in the formation of **2a** and **2b**.

(1) J. L. Strominger and D. J. Tipper, *Amer. J. Med.*, **39**, 708 (1965).
(2) R. Reiner and P. Zeller, *Helv. Chim. Acta*, **51**, 1905 (1968); G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, *J. Amer. Chem. Soc.*, **93**, 2342 (1971); M. R. Bell, R. Oesterlin, S. D. Clemans, and J. A. Carlson, Abstracts, XXIIIrd IUPAC Meeting, Boston, Mass., 1971, p 74; E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971).
(3) The name cephamycin has been proposed for 7-methoxy substituted cephalosporins.[4a] The excellent bioactivity of these compounds suggests the **7a** configuration. **1b** has been prepared using the methods of this paper (R. W. Ratcliffe and B. G. Christensen, manuscript in preparation) and is identical with the natural product, confirming this assignment.
(4) (a) 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; (b) 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).
(5) For an excellent recent review on structure–activity relationships, see M. L. Sassiver and A. Lewis, *Advan. Appl. Microbiol.*, **13**, 163 (1970). An alternate synthesis of 7-methoxy cephalosporins from the naturally occurring cephamycins is reported in an accompanying communication: S. Karady, S. H. Pines, L. M. Weinstock, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, *J. Amer. Chem. Soc.*, **94**, 1410 (1972).
(6) C. Rappe, *Acta Chem. Scand.*, **17**, 2140 (1963); J. P. Clayton, *J. Chem. Soc. C*, 2123 (1969); H. Baganz and H. May, *Chem. Ber.*, **99**, 3766 (1966); F. Weygand, H. J. Bestmann, and H. Fritsche, *ibid.*, **93**, 2340 (1960).
(7) D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, **50**, 1327 (1967).

Scheme I. Penicillin Flow Sheet



ture.[8] Hydrogenation of **3a** in ethyl acetate using 10% Pd/C afforded **4a** as an isolable intermediate. Phenylacetylation with phenylacetyl choride converted **4a** to benzyl-6-methoxybenzylpenicillin (**5a**): *m/e* 454; ir (film) 1780, 1750, 1690 cm^{-1}; $[\alpha]^{27}D$ +226° (*c* 1.08, CH_3OH). Sodium 6-methoxybenzylpenicillin (**5c**) was isolated when **5a** was hydrogenolyzed with 10% Pd/C in aqueous methanol in the presence of 1 equiv of $NaHCO_3$.

The 6-methoxy-6-epipenicillins are also available *via* a modification of the above route. Benzyl 6-diazopenicillanate, when stirred in MeOH–CH_2Cl_2 containing 1 equiv of NBA, was converted to a single benzyl 6β-bromo-6-methoxypenicillanate (**6a**):[9] mp 90–91°; ir (Nujol) 1780, 1730 cm^{-1}. This was equilibrated with LiBr in DMF at room temperature overnight giving a 1:3 mixture of **6a** and **6b** which were separated by chromatography on silica gel. **6b** (mp 41–43°; ir (Nujol) 1785, 1740 cm^{-1}) was converted to **3a** (90% purity) upon treatment with LiN_3 in DMF at room temperature. However, **6a** afforded a single new azido compound **3b** (ir (film) 2110, 1785, 1735 cm^{-1}) when

(8) The formation of a single methoxy azide, **3a**, from either bromo azide is presumed to occur by addition of methanol from the less-hindered exo face of the α-oxocarbonium ion: J. P. Begue and M. Charpentier Morize, *Angew. Chem., Int. Ed. Engl.*, **10**, 327 (1971), have recently described these intermediates. Although alternative mechanisms can be envisaged, this interpretion appears most reasonable.

(9) The formation of a single bromomethoxy compound **6a** is presumed to take place by attack at carbon by the bromonium ion, from the less-hindered exo face of the 6-diazopenicillanate, followed by displacement of nitrogen by methanol, with inversion, from the intermediate bromodiazonium ion.

Table II. Nmr Data of Cephalosporins ($CDCl_3$)

Compd	Chemical shift, τ (TMS)				
	C-2 (d of d)	C-3 methylene (d of d)	C-6	OCH_3	OAc
7	6.60	5.20	4.40		8.00
8a (major isomer)	6.62	5.06	5.30		8.00
9	6.61	5.08	5.17	6.40	8.00
10	6.65	5.05	5.17	6.50	8.01
11a	6.64	5.04	4.92	6.51	8.00
11c[a]	6.85	5.16	5.03	6.64	8.01

[a] DMSO was the solvent used with **11c**.

treated with the same reagent at 30–35° for 6 hr. Hydrogenation and phenylacetylation as before afforded benzyl-6-methoxy-6-epibenzylpenicillin (**5b**): ir (film) 1775, 1740, 1670 cm^{-1}; $[\alpha]^{27}D$ +86° (*c* 1, CH_3OH). Hydrogenolysis of **5b** in the presence of $NaHCO_3$ gave sodium 6-methoxy-6-epibenzylpenicillin (**5d**). Stereochemical assignments of the preceding penicillins were made on the basis of mechanistic considerations and nmr shifts,[10a] optical rotations,[10b] and the lower activity of **5d** (1% of **5c**).[11] Additional evidence supporting these assignments will be included in future publications.

7-Aminocephalosporanic acid *p*-toluenesulfonic acid salt was esterified with diphenyldiazomethane at room temperature. The benzhydryl ester in CH_2Cl_2 at 0° was converted by an aqueous solution of HNO_2 to benzhydryl 7-diazocephalosporanate (**7**) which was extracted into the organic phase and isolated as a glass: ir (film) 2080, 1790, and 1725 cm^{-1}. Bromine azide treatment, as in the penicillin series, yielded a mixture of bromo azides **8a** and **8b**: ir ($CHCl_3$) 2120, 1800, and 1740 cm^{-1}. Methanol in the presence of $AgBF_4$ converted the mixture to the methoxy azide **9** (mp 145–148°, ir ($CHCl_3$) 2120, 1785, and 1740 cm^{-1}) which in analogy to the methoxy azide **3a** is assigned the 7α-methoxy sterochemistry. Hydrogenation of **9** in dioxane using PtO_2 afforded **10**, which was readily acylated with 2-thienylacetyl chloride and pyridine in CH_2Cl_2 at 0° to afford **11a**: *m/e* 592 (M); ir (film) 1780, 1750, and 1690 cm^{-1}. Removal of the benzhydryl ester with TFA–anisole at 0° readily gave 7-methoxycephalothin (**11b**): uv (H_2O) 236 (ε 13,700), 263 nm (8600). Nmr data on these cephalosporin compounds are given in Table II.

5c is less active against microorganisms than benzylpenicillin; **11b**, however, exhibits much the same *in vitro* spectrum as cephalothin with the outstanding feature of inhibiting a number of cephalosporin-resistant organisms. This activity is presumed to be due at least in part to the resistance of 7-methoxy substituted cephalosporins to various β-lactamases.[12]

(10) (a) The nmr shifts of the 5-hydrogens in the bromo compounds **2a,b**, **6a,b**, and the 6,6-dibromopenicillanate are consistent with the hypothesis that bromine cis to the 5-H causes a considerable downfield shift suggesting a 6α-bromo configuration for **6b** (see Table I). The formation of the methoxy azides **3a** and **3b** from **6b** and **6a**, respectively, is consistent with displacement of bromide by azide with inversion, leading to the assigned configuration. (b) $[\alpha]^{27}D$ +213° (*c* 1.09, CH_3OH) is reported for benzyl penicillin G: H. T. Clarke, J. R. Johnson, and Sir R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p 94. Benzyl epipenicillin G prepared in our laboratories by an independent procedure shows $[\alpha]^{27}D$ +160.9° (*c* 0.99, CH_3OH).

(11) D. A. Johnson and D. Mania, *Tetrahedron Lett.*, 267 (1969), and T. Sawai, T. Saito, and S. Mitsuhashi, *J. Antibiot.*, **23**, 488 (1970), both report the decreased activity of epipenicillins.

Extensive modifications of the methoxyl-substituted 6-APA and 7-ACA nuclei have been made by using other acyl side chains and replacement of the C-3 acetate in the cephalosporin series by other functionalities. Since this methodology also allows the introduction of groups at C-6(7) other than methoxyl, a wide variety of new penicillins and cephalosporins have become available. These changes will be the subject of forthcoming communications from these laboratories.

Acknowledgment. The authors thank Drs. S. Karady and M. Sletzinger of these laboratories for helpful discussions during the course of this work. We also thank Dr. R. A. Firestone and J. S. Amato for initially preparing compounds **7** and **8**.

(12) D. Hendlin and coworkers, unpublished results.

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Semisynthetic Cephalosporins *via* a Novel Acyl Exchange Reaction

Sir:

Cephamycin C (**1**),[1] a new member of the cephalosporin family of antibiotics, possesses a high resistance toward β-lactamase enzymes as well as good activity against gram-negative and modest activity against gram-positive bacteria.

We wish to report a novel sequence for the exchange of the aminoadipoyl side chain for other acyl groups, which permits the synthesis of analogs[2] with wider antibiotic spectra. This sequence is equally useful for the conversion of cephalosporin C to other acyl analogs, and in contrast to the previous methods, does not require the formation of 7-aminocephalosporanic acid.[3]

The reaction of **2** with an acid chloride and *N*-trimethylsilyltrifluoroacetamide in methylene chloride produces the diacyl derivatives **3** in over 75% yield. Neither

(1) (a) E. O. Stapley, D. Hendlin, S. Hernandez, M. Jackson, J. M. Mata, A. K. Miller, H. B. Woodruff, T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter, F. J. Wolf, G. Albers-Schonberg, B. H. Arison, and J. L. Smith, 11th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N. J., 1971, Abstract No. 15; (b) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehm, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971).

(2) An alternate synthesis of 7-methoxycephalosporins is described by: L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *ibid.*, **94**, 1408 (1972).

(3) E. van Heyningen, *Advan. Drug Res.*, **4**, 22 (1967).