

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:

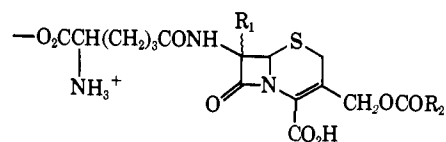
It has been suggested that an α -methyl group at C-6 of the penicillin nucleus would enhance antibacterial activity.¹ Several groups have attempted modifications at this position.² Recently we have developed synthetic routes to 6-methoxypenicillins and 7-methoxycephalosporins. Our interest in these compounds also arises from the discovery of four members of the cephamycin³ class (1a-d), each of which contains a 7-methoxyl substituent.⁴ Like cephalosporin C (1e), these new ce-

(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.^{4b} 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-Schon-



- 1a, R₁ = OCH₃; R₂ = NH₂
 1b, R₁ = OCH₃; R₂ = CH₃
 1c, R₁ = OCH₃; R₂ = -C(OCH₃)=CHC₆H₄OH·p
 1d, R₁ = OCH₃; R₂ = -C(OCH₃)=CHC₆H₄OSO₃⁻·p
 1e, R₁ = H; R₂ = CH₃

phalosporins contain an α -amino adipoyl 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.

Although the reactions of aliphatic diazocarbonyl compounds with halogens and pseudohalogens⁶ are well known, their reaction with bromine azide has not been reported. Treatment of benzyl 6-diazopenicillanate⁷ 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 6 β -azido-6-methoxypenicillanate (3a): mp 60-61°; ir (CH₂Cl₂) 2125, 1785, 1750 cm^{-1} , upon treatment with AgBF₄ in methanol at room tempera-

Table I. Nmr Data of Penicillins (CDCl₃)

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-dibromo- penicillanate ^b	4.20	5.44	8.41, 8.62	

^a D₂O was the solvent used with 5c and 5d. ^b Obtained as a by-product in the formation of 2a and 2b.

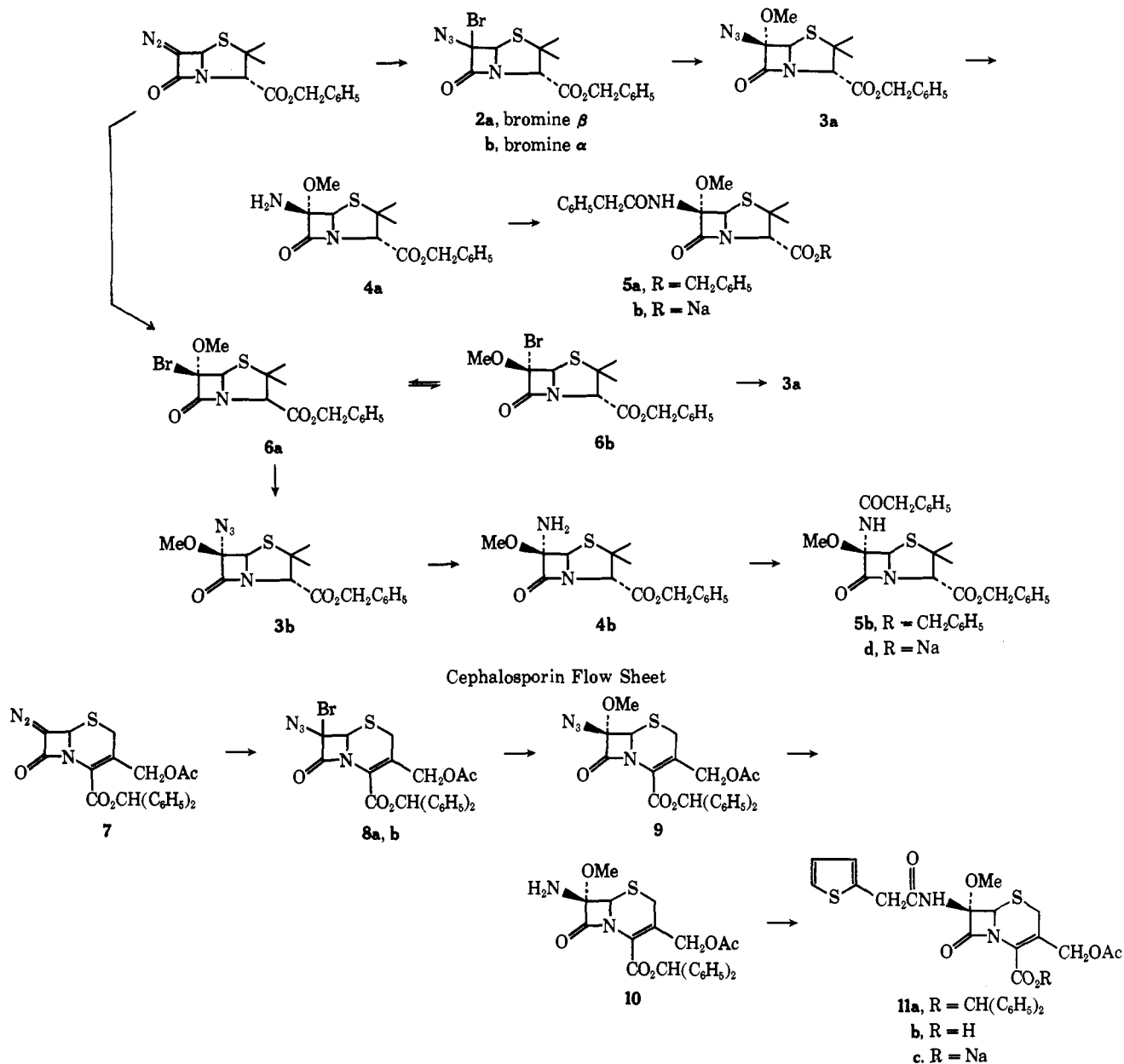
berg, B. H. Arison, and J. L. Smith, Abstracts, XIth Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N.J., 1971, p 8; (b) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971).

(5) For an excellent recent review on structure-activity relationships, see M. L. Sasser 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. Sletzing, *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 chloride converted **4a** to benzyl-6-methoxybenzylpenicillin (**5a**): *m/e* 454; ir (film) 1780, 1750, 1690 cm⁻¹; [α]_D²⁷ +226° (c 1.08, CH₃OH). Sodium 6-methoxybenzylpenicillin (**5c**) was isolated when **5a** was hydrogenolyzed with 10% Pd/C in aqueous methanol in the presence of 1 equiv of NaHCO₃.

The 6-methoxy-6-epipenicillins are also available via a modification of the above route. Benzyl 6-diazo-

(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 -oxocarbenium 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 interpretation appears most reasonable.

penicillanate, when stirred in MeOH-CH₂Cl₂ containing 1 equiv of NBA, was converted to a single benzyl 6 β -bromo-6-methoxybenzylpenicillanate (**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 LiN₃ in DMF at room temperature. However, **6a** afforded a single new azido compound **3b** (ir (film) 2110, 1785, 1735 cm⁻¹) when

(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 (CDCl₃)

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; [α]_D²⁵ +86° (c 1, CH₃OH). Hydrogenolysis of **5b** in the presence of NaHCO₃ 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 CH₂Cl₂ at 0° was converted by an aqueous solution of HNO₂ 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 (CHCl₃) 2120, 1800, and 1740 cm⁻¹. Methanol in the presence of AgBF₄ converted the mixture to the methoxy azide **9** (mp 145–148°, ir (CHCl₃) 2120, 1785, and 1740 cm⁻¹) which in analogy to the methoxy azide **3a** is assigned the 7 α -methoxy stereochemistry. Hydrogenation of **9** in dioxane using PtO₂ afforded **10**, which was readily acylated with 2-thienylacetyl chloride and pyridine in CH₂Cl₂ 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 (H₂O) 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 6 α -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) [α]_D²⁵ +213° (c 1.09, CH₃OH) 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 [α]_D²⁵ +160.9° (c 0.99, CH₃OH).

(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.

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

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Semisynthetic Cephalosporins via a Novel Acyl Exchange Reaction

Sir:

Cepharmycin 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 amino adipoyl side chain for other acyl groups, which permits the synthesis of analogs² 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. Higgins, M. M. Hoehn, 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).