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]

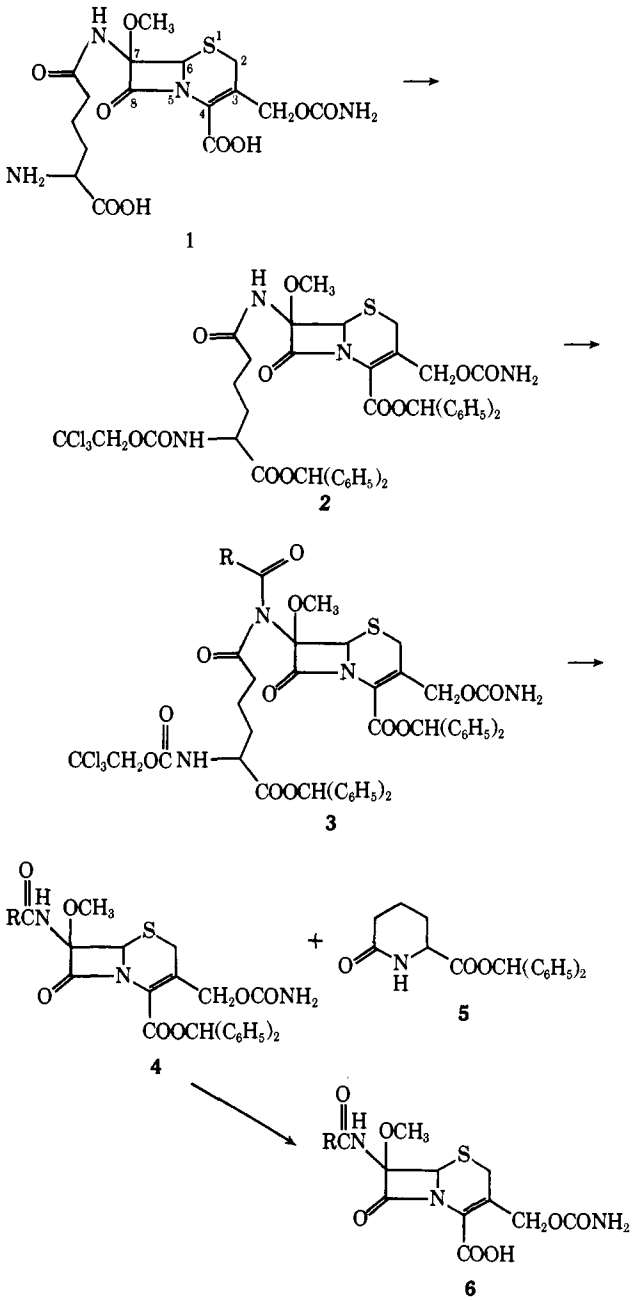
The reaction of **2** with an acid chloride and *N*-trimethylsilyltrifluoroacetamide in methylene chloride produces the diacyl derivatives **3** in over 75% yield. Neither

(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).

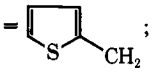
(2) An alternate synthesis of 7-methoxycephalosporins is described by: L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *ibid.*, **94**, 1408 (1972).

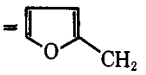
(3) E. van Heyningen, *Advan. Drug Res.*, **4**, 22 (1967).

Scheme I



6a, R = $C_6H_5CH_2$; mp 159–161° dec

6b, R =  ; mp 149–150° dec

6c, R =  ; mp 156–161° dec

6d, R = $C_6H_5SCH_2$; mp 119–123° dec

double bond isomerization nor acylation of either of the urethane functions occurs under these conditions. A discussion of this new reaction for the acylation of amides will be published elsewhere.

The removal of the nitrogen protecting group initiates the selective cleavage of the aminoadipoyl side chain by spontaneous cyclization to lactam **5**, with the expulsion of the esters of the new antibiotics **4** in over 80% yield. Ester deblocking provides the bioactive acids **6** listed above (Scheme I).

The experimental procedure is exemplified by the preparation of the phenylacetyl analog **6a**. Cephamycin C was converted to its trichloroethoxycarbonyl (TROC)[4] derivative in pH 8.5–9 phosphate buffer, and the crude product alkylated with diphenyldiazomethane[5] to give the TROC diester **2**, obtained after chromatographic purification as a noncrystalline foam: $[\alpha]_D$ 59° (c 1, MeOH); uv 265 nm (ϵ 6520); nmr ($CDCl_3$) δ 1.85 (m, 4, C(O)CH_2CH_2), 2.30 (m, 2, CH_2C(NH)COO), 3.10–3.50 (AB, J = 18 Hz, 2, SCH_2), 3.5 (s, 3, OCH_3), 4.70 (s, 2, CCl_3CH_2), 4.8–5.0 (m, 5, CH_2OCONH_2 and HC(COO)NH), 5.02 (s, 1, C_6H), 6.0 (d, 1, J = 8 Hz, CNHOCO), 6.9 (s, 2, $(C_6H_5)_2CH$), 7.0–7.6 (m, 20, $(C_6H_5)_2C$). When this substrate was treated with 4 mol equiv each of phenylacetyl chloride and *N*-trimethylsilyltrifluoroacetamide in methylene chloride for 16 hr at 40°, imide **3a** formed: nmr ($CDCl_3$) δ 1.85 (m, 4, $COCH_2CH_2$), 2.3 (m, CH_2C(NH)COO), 3.35 (br d, SCH_2), 3.50 (s, 3, OCH_3), 3.95 (s, 2, $C_6H_5CH_2CO$), 4.70 (s, 2, CCl_3CH_2), 4.8–5.0 (m, 5, CH_2OCONH_2 and HC(COO)NH), 5.02 (s, 1, C_6H), 5.7 (d, 1, J = 8 Hz, CNHOCO), 6.9 (s, 2, $(C_6H_5)_2CH$), 7.0–7.6 (m, 25, C_6H_5). On treatment of **3a** with zinc in 90% acetic acid, followed by chromatography, there was obtained the benzhydryl ester of the 7-phenylacetyl analog **4a** (uv max (MeOH) 265 nm (ϵ 5870); nmr ($CDCl_3$) δ 3.30 (br d, 2, SCH_2), 3.40 (s, 3, OCH_3), 3.60 (s, 2, $C_6H_5CH_2CO$), 4.7–5.0 (m, 4, CH_2OCONH_2), 5.0 (s, 1, C_6H), 6.85 (s, 1, $(C_6H_5)_2CH$), 7.0–7.5 (m, 15, C_6H_5), and benzhydryl 2-piperidone-6-carboxylate (**5**). Treatment of **4a** with trifluoroacetic acid and anisole[5] for 1 min at 0° provided the free carboxylic acid **6a**: mp 159–161° dec (ethyl acetate); uv max (pH 7 buffer) 267 nm (ϵ 8650); ir (CH_3CN) 1780, 1735, 1700 cm^{-1}; nmr (CD_3CN) δ 3.40 (br d, 2, CH_2S), 3.42 (s, 3, OCH_3), 3.65 (s, 2, $C_6H_5CH_2CO$), 4.90 (q, 2, CH_2O), 4.90 (s, 2, NH_2), 5.00 (s, 1, C_6H), 7.30 (s, 5, C_6H_5).

By similar reactions, cephalosporin C was converted to cephalothin, mp 164° dec, identical in all chemical and biological respects with an authentic sample.[6]

The same procedure was used for the preparation of analogs **6b**, **6c**, and **6d**. Analogous spectral characteristics and satisfactory elemental analyses were used for their identification. The biological properties of these new antibiotics will be reported elsewhere.

Acknowledgment. The authors thank Drs. B. Christensen and L. Cama of these laboratories for helpful discussions during the course of this work. We are indebted to Drs. B. H. Arison and A. K. Douglas and Messrs. D. V. Harris and R. C. Zerfing for obtaining the nmr spectra.

(4) (a) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbüggen, *J. Amer. Chem. Soc.*, **88**, 852 (1966); (b) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).

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(6) Prepared from Keflin, a product of Eli Lilly and Co.

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Received November 9, 1971