debenzoylation of **4a** and **5a** with methanolic ammonium hydroxide followed by heating the resulting nucleosides **4b** and **5b** in dimethylformamide at 140° for 16 hr. Under these conditions, **4b**, like nucleocidin itself, formed an ionic N^3,5′ cyclonucleoside characterized by its uv spectrum (λ_{max} 274 nm) and its electrophoretic mobility, while **5b** remained unchanged.

While the iodo function of **4a** was readily removed by catalytic hydrogenolysis giving the corresponding 5′-deoxy-4′-fluoronucleoside with λ_{max} 250 (ϵ 22,300), 273 nm (ϵ 16,800); nmr ($CDCl_3$) 1.65 (d, 3, $J_{H,F}$ = 17 Hz, $C_{5'}H_3$) 6.30 (br s, 1, $J_{1',2'} \simeq 1$ Hz, $C_{1'}H$), 8.13 and 8.69 (s, 1, C_2H and C_8H), its nucleophilic displacement proved to be very difficult. None of the oxygen nucleophiles tried proved satisfactory but reaction of **4a** with lithium azide in dimethylformamide at 100° for 20 hr followed by debenzoylation with methanolic ammonia gave 5′-azido-5′-deoxy-4′-fluoro-2′,3′-*O*-isopropylideneadenosine (**6**) in 93% yield: λ_{max}^{MeOH} 258 nm (ϵ 13,300); λ_{max} (KBr) 4.70 μ (N_3); nmr ($CDCl_3$) 3.61 (d, 2, $J_{H,F}$ = 13.5 Hz, $C_{5'}H_2$), 5.58 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{3',F}$ = 12.5 Hz, $C_{3'}H$), 6.38 (s, 1, $C_{1'}H$), 7.93 and 8.41 ppm (s, 1, C_2H and C_8H).[7] While catalytic reduction of the azido function of **6** and its N^6-benzoyl derivative to the corresponding 5′-amino-4′-fluoronucleosides was readily achieved, subsequent attempted deamination with nitrous acid led to complex mixtures.

Conversion of the azido function of **6** to the desired hydroxyl group was achieved by ultraviolet irradiation of a benzene solution of **6** in a Pyrex apparatus.[8] The resulting intermediate 5′-imine was hydrolyzed to the 5′-aldehyde by brief acidic treatment and then directly reduced with sodium borohydride giving 4′-fluoro-2′,3′-*O*-isopropylideneadenosine (**7a**) with mp 225–226° from methanol: λ_{max}^{MeOH} 258 nm (ϵ 13,200); ORD (MeOH) negative Cotton effect with $[\Phi]_{280}^{tr}$ −2000°, $[\Phi]_{263}$ 0°, and $[\Phi]_{230}^{pk}$ +3800°; nmr (pyridine-d_5) 4.19 (d, 2, $J_{H,F}$ = 9.5 Hz, $C_{5'}H_2$), 5.90 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{3',F}$ = 12 Hz, $C_{3'}H$), 6.90 (s, 1, $C_{1'}H$), 8.45 and 8.56 ppm (s, 1, C_2H and C_8H).

The reactions of **7a** with sulfamoyl chloride using either pyridine or sodium hydride as base[9] gave the 5′-sulfamate **7c** in low yields. If, however, **7a** was first treated with an excess of bis(tributyltin) oxide in refluxing benzene with azeotropic removal of water it was converted into the corresponding 5′-*O*-tributyltin ether (**7b**). Without isolation this compound was treated[10] with sulfamoyl chloride at 5° for 10 min giving the 5′-*O*-sulfamate **7c** in 87% yield as the hydrate with mp 162–165° from water: λ_{max}^{MeOH} 259 nm (ϵ 15,800); nmr (pyridine-d_5) 4.9 (ABX multiplet, 2, $C_{5'}H_2$ deshielded 0.70 ppm relative to **7a**), 5.92 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{3',F}$ = 12 Hz, $C_{3'}H$), 6.86 (s, 1, $C_{1'}H$), 8.46 and 8.51 ppm (s, 1, C_2H and C_8H). Treatment of **7c** with 90% trifluoroacetic acid at 23° for 30 min gave 4′-fluoro-5′-*O*-sulfamoyladenosine (**8**) as the monohydrate in 60% yield after two recrystallizations from water: mp >190° dec; picrate mp 145–147° (lit.[1] mp 143–144°); λ_{max}^{MeOH} 259 nm (ϵ 15,000); nmr (pyridine-d_5) 5.03 (d, 2, $J_{H,F}$ = 8.5 Hz, $C_{5'}H_2$), 5.25 (q, 1, $J_{1',2'}$ = 2 Hz, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 5.56 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{3',F}$ = 17.5 Hz, $C_{3'}H$), 6.94 (d, 1, $J_{1',2'}$ = 2 Hz, $C_{1'}H$), 8.24 (br s, 2, C_6NH_2), 8.49 and 8.51 ppm (s, 1, C_2H and C_8H) as described for nucleocidin.[2] The antibacterial spectrum of synthetic **8** was very similar to what has been reported for natural nucleocidin.[1]

The above series of reactions has also been carried out in the α-L-lyxofuranosyl series starting with **5**. These results, together with the preparation of some analogs of nucleocidin, will be described in full at a later date.

(8) Photochemical conversions of primary sugar azides to aldehydes have been described: D. Horton, A. E. Luetzow, and J. C. Wease, *Carbohyd. Res.*, **8**, 366 (1968).

(9) These methods have been successfully used for sulfamation of 2′,3′-*O*-isopropylideneadenosine: D. A. Shuman, M. J. Robins, and R. K. Robins, *J. Amer. Chem. Soc.*, **92**, 3434 (1970).

(10) See, *e.g.*, J. Valade and M. Peregre, *C. R. Acad. Sci.*, **254**, 3693 (1962). Other examples of activation of nucleoside hydroxyl groups *via* tin derivatives will be described elsewhere: D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, unpublished results.

(11) Syntex Postdoctoral Fellow, 1969–1971.

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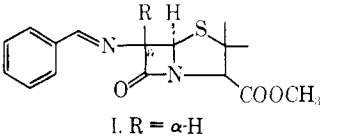
6-Methyl Penicillins and 7-Methyl Cephalosporins

Sir:

It has been well established[1,2] that penicillins and cephalosporins inhibit bacterial cell-wall synthesis by interfering with the final cross-linking process, which has been termed transpeptidation and involves an amino group in a peptidoglycan molecule and the D-alanyl-D-alanine end of the acetyl-muramyl pentapeptide fragment in another. It has been suggested that the chemical structures of both penicillins and cephalosporins can mimic this D-alanyl-D-alanine residue and thereby inhibit (irreversibly) the enzyme transpeptidase responsible for the cross-linking. 6-Methyl penicillins and 7-methyl cephalosporins have been proposed[1] as more analogous to D-alanyl-D-alanine than their parent molecules, since both classes bear a methyl group in the same position as is found in the D-alanyl residue. It has been suggested that they may, therefore, show enhanced effectiveness as antibacterial agents. To examine this hypothesis, we have synthesized both a 6-methyl penicillin and a 7-methyl cephalosporin.

6-Methyl-6-phenylacetamidopenicillanic acid, methyl ester (V) was prepared by the following sequence of reac-



I. R = α-H
II. R = α-CH_3
III. R = β-CH_3

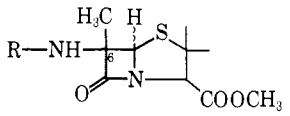
tions. Treatment of *N*-benzylidene-6-aminopenicillanic acid, methyl ester (I) with 1 equiv of sodium hydride and excess methyl iodide in dimethoxyethane at 0° gave a mixture of epimeric 6-methyl derivatives [II, 90% yield; nmr ($CDCl_3$) 522 (s, 1 H), 322 (s, 1 H), 108 (s, 3 H) Hz; III, 5% yield; nmr ($CDCl_3$), 516 (s, 1 H), 329 (s, 1 H), 268 (s, 1 H) Hz]. Crystallization from dichloromethane–hexane gave white, solid II (mp 83–

(1) J. L. Strominger and D. J. Tipper, *Amer. J. Med.*, **39**, 708 (1965).

(2) J. L. Strominger, K. Izaki, M. Matsuhasi, and D. Tipper, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **26**, 9 (1967).

84°). Acidic hydrolysis of II gave an almost quantitative yield of 6-amino-6-methyl penicillanic acid, methyl ester (IV). The stereochemical course of the alkylation reaction, expected to result in preferential methylation of the sterically less-hindered side of the 6-anion, was demonstrated through a single-crystal X-ray analysis of IV (mp 94–95°, $a = 6.51$, $b = 6.80$, $c = 14.17$ Å, $\beta = 99.75°$, space group $P2_1$, $Z = 2$). The subtle crystallographic distinction between the 6α-methyl and the 6β-amino substituents of this structure was made on the basis of their relative electron densities and temperature factors and, most convincingly, through an examination of the molecular crystal packing. Molecular association about the screw axis results in an *inter*molecular 6-amine–lactam carbonyl oxygen atom distance of 3.0 Å, whereas the shortest intermolecular contact of the 6-methyl substituent is 3.6 Å. (Final $R = 0.09$ for the 524 nonzero reflections).[3]

Acylation of IV in dichloromethane with phenylacetyl chloride and base gave the desired 6α-methyl-6-phenylacetamidopenicillanic acid, methyl ester (V) [mp



IV, R = H, α-methyl at C_6

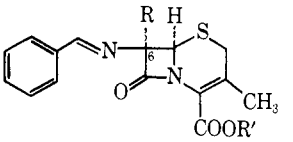
V, R = $C(=O)CH_2C_6H_5$, α-methyl at C_6

VI, R = $C(=O)CH_2C_6H_5$, β-methyl at C_6

107–110°; nmr ($CDCl_3$) 436 (s, 5 H), 375 (s, 1 H), 322 (s, 1 H), 260 (s, 1 H), 224 (s, 3 H), 213 (s, 2 H), 104 (s, 3 H), 86 (s, 6 H) Hz, in better than 90% yield]. The 6β isomer VI [nmr ($CDCl_3$) 442 (s, 5 H), 366 (s, 1 H), 344 (s, 1 H), 267 (s, 1 H), 230 (s, 3 H), 219 (s, 2 H), 98 (s, 3 H), 94 (s, 3 H), 91 (s, 3 H) Hz] was prepared by first hydrolyzing the mother liquors from the crystallization of *N*-benzylidene-6-amino-6α-methylpenicillanic acid, methyl ester (II), followed by the acylation of this crude product with phenylacetyl chloride. The resulting mixture was carefully purified through preparative silica gel thin-layer chromatography to give VI in small quantity as an oil.

Basic hydrolysis of 6α-methyl-6-phenylacetamidopenicillanic acid, methyl ester (V) has so far been unsuccessful.

7α-Methyl-7-phenoxyacetamidodesacetoxycephalosporanic acid, methyl and *tert*-butyl esters (XI and XII, respectively), were synthesized in a similar sequence of reactions: the corresponding *N*-benzylidene-7-aminodesacetoxycephalosporanic acid esters, VII and VIII, were alkylated with methyl iodide to give the corresponding esters [IX, methyl ester; oil; nmr ($CDCl_3$), 524 (s, 1 H), 454 (m, 5 H), 282 (s, 1 H), 232 (s, 3 H), 202 (t, 2 H), 223 (s, 3 H), 109 (s, 3 H) Hz; and X, *tert*-butyl ester; mp 138–140°; nmr ($CDCl_3$) 511 (s, 1 H), 284 (s, 1 H), 187 (q, 2 H), 116 (s, 3 H), 98 (s, 3 H), 84 (s, 9 H) Hz] of *N*-benzylidene-7α-methyl-7-aminodesacetoxycephalosporanic acid in better than 80% yields. The configuration at C_7 was assigned to the major product in analogy to the 6α-methyl penicillin series. Again, about 15% of the respective β isomers could be detected by nuclear magnetic resonance spectroscopy.



VII, R = H; R′ = CH_3

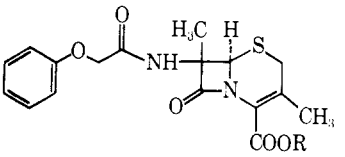
VIII, R = H; R′ = $C(CH_3)_3$

IX, R = CH_3; R′ = CH_3

X, R = CH_3; R′ = $C(CH_3)_3$

Both IX and X were acylated directly, using phenoxyacetyl chloride in aqueous chloroform, to give 7α-methyl-7-phenoxyacetamidodesacetoxycephalosporanic acid, methyl ester (XI) and 7α-methyl-7-phenoxyacetamidodesacetoxycephalosporanic acid, *tert*-butyl ester (XII), respectively, in better than 85% yields.

The 7β isomer of the *tert*-butyl ester XIII was isolated by preparative silica gel thin-layer chromatography of the acylated mother liquors of recrystallized X.



XI, R = CH_3, α-methyl at C_7

XII, R = $C(CH_3)_3$, α-methyl at C_7

XIII, R = $C(CH_3)_3$, β-methyl at C_7

XIV, R = H, α-methyl at C_7

7α-Methyl-7-phenoxyacetamidodesacetoxycephalosporanic acid (XIV) (oil; nmr ($CDCl_3$) 577 (s, 1 H), 429 (m, 5 H), 288 (s, 1 H), 273 (s, 2 H), 184 (s, 2 H), 130 (s, 3 H), 111 (s, 3 H) Hz) was prepared by treating the parent *tert*-butyl ester XII with trifluoroacetic acid for 2 min at 0°. The desired acid was recovered in only 25% yield.

To ascertain their biological activities, both the α and β isomers of 6-methyl-6-phenylacetamidopenicillanic acid, methyl ester (V and VI) were compared with penicillin G methyl ester in a disk assay on *Staphylococcus aureus* 209 P agar plates. Initial results indicated that both isomers were inactive against this organism at a concentration of 500 μg/ml, whereas penicillin G methyl ester was active at 8 μg/ml. It is well known[4] that in the mouse, penicillin G methyl ester is as active as its free acid. Therefore, penicillin G methyl ester and the 6α-methyl penicillin G methyl ester V were compared *in vivo* in the mouse against *Streptococcus pyogenes*, being administered parenterally. Penicillin G was active at 25 mg/kg, whereas the 6α-methyl penicillin G methyl ester showed no activity, even at 325 mg/kg against the same organism. Similarly, 7α-methyl-7-phenoxyacetamidodesacetoxycephalosporanic acid, methyl ester showed no activity on a *Staphylococcus aureus* 209 P agar plate. 7α-Methyl-7-phenoxyacetamidodesacetoxycephalosporanic acid (XIV) showed activity only at 1250 μg/ml on a *Staphylococcus aureus* 209 P agar plate, while its parent cephalosporin, 7-phenoxyacetamidodesacetoxycephalosporanic acid, was active at 15 μg/ml. In a tube dilution assay, XIV showed an MIC

(3) Tables of observed and calculated structure amplitudes and atomic coordinates from this analysis have been deposited as Document No. NAPS-01568 with the ASIS National Auxiliary Publication Service, c/o CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022. A copy may be secured by citing the document number and by remitting $5.00 for photocopies or $2.00 for microfiche. Advanced payment is required. Make check or money order payable to ASIS–NAPS.

(4) A. P. Richardson, H. A. Walker, I. Miller, and R, Hansen, *Proc. Soc. Exp. Biol. Med.*, **60**, 272 (1945).

(minimum inhibitory concentration) of 50 μg/ml against both *Staphylococcus aureus* SC 2399 and *Streptococcus pyogenes* SC 3862. The MIC of the parent cephalosporin against the same two organisms was 1 μg/ml. More extensive biological evaluation is in progress.

Further experiments are needed to determine to what extent the present results will require refinement or alteration of the proposed mechanism of inhibition[1,2] of bacterial enzymes by β-lactam antibiotics.[5]

Acknowledgment. We are indebted to Felix Pansy and Harold Basch for biological data and to Dr. Allen Cohen and Dr. M. Puar for spectroscopic data. We are especially thankful to Professor Strominger, who suggested the problem to us and has enthusiastically followed our work.

(5) NOTE ADDED IN PROOF. It is interesting to note that the 7-methoxycephalosporin C which has been isolated by R. Nagarajan, *et al.* (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)) is reported to be more active toward gram negative organisms than is cephalosporin C.

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A New Method for the 1,4 Addition of the Methylenecarbonyl Unit (-CH_2CO-) to Dienes

Sir:

Since the reaction of ketenes with 1,3-dienes leads to cyclobutanone formation rather than Diels–Alder addition,[1] other approaches are required for the synthesis of structures corresponding to the 1,4 addition of the -CH_2CO- unit to 1,3-dienes. The use of sequences involving the addition of 2-acetoxyacrylonitrile[2] and 2-chloroacrylonitrile[3,4] as dienophiles has been described for cyclopentadiene (and also cyclohexadiene in the case of the latter). However, these dienophiles are of only moderate reactivity and appear to be of limited utility with sensitive or less reactive dienes. Further, the requirement of strong base for the conversion of the initial adduct into the corresponding ketone precludes the use of this method for the synthesis of Δ^3-cyclohexenones from acyclic dienes.

The discovery that the reaction of 2-chloroacrylonitrile with dienes is strongly catalyzed by dry cupric fluoroborate led to the successful synthesis of the 7-substituted bicyclo[2.2.1]heptenones Ia and Ib from the corresponding 5-monosubstituted cyclopentadienes.[5,6] This process represents the first example of the successful use of a 5-monosubstituted cyclopentadiene in this way and a key initial stage of the synthesis of the natural primary prostaglandins.[7-9] Although the cupric-catalyzed Diels–Alder addition extends the applicability of 2-chloroacrylonitrile to certain sensitive dienes, our interest in the general synthetic problem and the development of optimum synthetic routes to prostanoids[10] has prompted further studies in this area. These have led to the excellent general method which is described herein.

The readily accessible 2-chloroacrylyl chloride[11,12] exhibits high dienophilic reactivity (comparable to maleic anhydride) and further, because of its geminate substitution, reacts selectively with various 5-substituted cyclopentadienes (without prototropic isomerization) to form adducts in which the 7 substituent is *exclusively* anti to the bridge bearing the chloro and chloroformyl groups.[13] The effectiveness of 2-chloroacrylyl chloride as a dienophile and a process for the conversion of the resulting adducts to ketones by replacement of Cl and COCl by oxygen can be illustrated by the synthesis of the keto benzyl ether Ia *without isolation of intermediates.* An ethereal solution of 5-benzyloxymethylcyclopentadiene[6] (*ca.* 1 *M*) and 2-chloroacrylyl chloride at 0° for 18 hr furnished the adduct IIa (as a 2:1 mixture of exo and endo acid chlorides by nmr analysis) in *ca.* 99% yield. Treatment of IIa with sodium azide in dimethoxyethane gave the corresponding acyl azide which upon heating underwent Curtius rearrangement to the isocyanate, leading finally after hydrolysis with aqueous acetic acid to the bicyclic ketone Ia in *ca.* 90% yield (overall for the five reactions from cyclopentadiene and chloromethylbenzyl ether). The ease of operation and practicality of this synthesis can be seen from the following experimental procedure which is given as a model.

7-*syn*-Benzyloxymethyl-2-norbornen-5-one (Ia). Chloromethyl benzyl ether (15.65 g) was added over 20 min to a cooled (−22 to −20°), stirred slurry of thallous cyclopentadienide[6] in 40 ml of dry ether (under argon). After 7 hr the mixture was filtered (at below −20°), the solid (TlCl) was washed with dry ether (three 20-ml portions), and the combined chilled ethereal solution was treated with 2-chloroacrylyl chloride (16.25 g). After 18 hr at 0°, the solvent was removed under reduced pressure to afford the Diels–Alder adduct (30.82 g, 99%) as a colorless oil.[14a] A solution of the adduct in 306 ml of dry dimethoxyethane was stirred with 12.8 g of sodium azide at 25° for 1.5 hr, and the mixture was filtered. The filtrate was heated to reflux for 2 hr, cooled to 25°, and treated with 60 ml of acetic acid–water (2:1) at 55–60° until infrared analysis of an aliquot indicated the lack of isocyanate absorp-

(1) See, for example, J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 1 (1962).
(2) P. D. Bartlett and B. E. Tate, *J. Amer. Chem. Soc.*, **78**, 2473 (1956).
(3) H. Krieger, *Suom. Kemstilehti B*, **36**, 68 (1963); J. Paasivirta and H. Krieger, *ibid.*, *B*, **38**, 182 (1965); J. Paasivirta, *ibid.*, *A*, **39**, 120 (1966).
(4) P. K. Freeman, D. M. Balls, and D. J. Brown, *J. Org. Chem.*, **33**, 2211 (1968).
(5) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).
(6) E. J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971).
(7) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970).
(8) E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970).
(9) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971).
(10) We have found this to be a useful term which can be applied to designate the whole family (superset) of natural prostaglandins and prostaglandin-like compounds.
(11) C. S. Marvel, J. Dec, H. G. Cooke, Jr., and J. C. Cowan, *J. Amer. Chem. Soc.*, **62**, 3495 (1940).
(12) M. Seefelder, German Patent 1,167,819 (April 1964); *Chem. Abstr.*, **61**, 1761 (1964).
(13) Not surprisingly, maleic anhydride and dimethyl acetylenedicarboxylate add to 5-monosubstituted cyclopentadienes to afford mixtures of 7-syn and 7-anti isomers.
(14) (a) Infrared and nmr spectra were in agreement with the assigned structure. (b) Satisfactory analytical data were obtained for this intermediate.