ring rheadans from appropriate phthalideisoquinoline alkaloids.

Acknowledgment. We are indebted to our Physical Chemistry Department, under the direction of Dr. R. P. W. Scott, for the spectral and analytical data. We are grateful to Mr. J. Borgese and Mrs. J. Cheung for technical assistance and to Professor G. Büchi, Massachusetts Institute of Technology, for fruitful discussions.

(8) Visiting Professor, Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck, Austria.

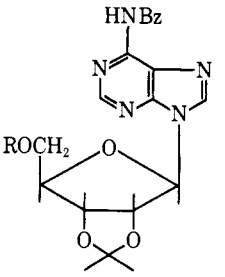
W. Klötzer,[8] S. Teitel, J. F. Blount, A. Brossi*
Chemical Research Department, Hoffmann-La Roche Inc.
Nutley, New Jersey 07110
Received May 29, 1971

Synthesis of the Nucleoside Antibiotic Nucleocidin

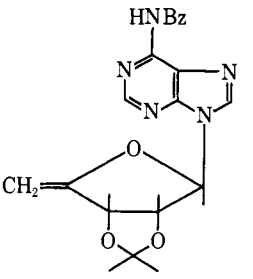
Sir:

Nucleocidin, a fairly broad spectrum antibacterial and antitrypanosomal agent elaborated by *Streptomyces calvus*,[1] has been shown to have the structure 4′-fluoro-5′-*O*-sulfamoyladenosine (**8**) although the D-ribo configuration has never been unequivocally proved.[2] This structure is of particular interest since nucleocidin is the first naturally occurring derivative of a fluoro sugar. We now wish to report a synthesis of this compound which also confirms the proposed structure.

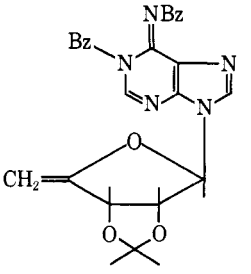
Reaction of N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine (**1a**)[3] with methanesulfonyl chloride gave the 5′-*O*-mesyl derivative **1b** which was not purified but rather directly treated with potassium *tert*-butoxide in tetrahydrofuran to give 6-benzamido-9-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)-purine (**2**)[4] in a yield of 60% from **1a**: mp 151–153° (benzene); λ_{max}^{MeOH} 230 (ε 13,700), 279 nm (ε 21,400); nmr ($CDCl_3$) 4.53 (d, 1, J_{gem} = 2.5 Hz, $C_{5'a}H$), 4.67 (q, 1, J_{gem} = 2.5 Hz, $J_{3',5'b}$ = 1 Hz, $C_{5'b}H$), 6.31 (s, 1, $C_{1'}H$), 8.05 and 8.77 ppm (s, 1, C_2H and C_8H). Treatment of **2** with benzoyl chloride in pyridine gave the dibenzoyl olefin **3** as a homogeneous foam isolated by chromatography on silicic acid in 90% yield: $\lambda_{max}^{dioxane}$ 249 (ε 21,900), 276 nm (ε 16,900); nmr ($CDCl_3$) 4.49 (d, 1, J_{gem} = 2.5 Hz, $C_{5'a}H$), 4.64 (q, 1, J_{gem} = 2.5 Hz, $J_{3',5'b}$ = 1 Hz, $C_{5'b}H$), 6.33 (s, 1, $C_{1'}H$), 8.12 and 8.68 ppm (s, 1, C_2H and C_8H). The addition of iodine (4 equiv) to a vigorously stirred solution of **3** (1 equiv) in nitromethane, tetrahydrofuran, or methylene chloride in the presence of freshly ground silver fluoride (5 equiv) led to a mixture of the epimeric 5′-deoxy-4′-fluoro-5′-iodonucleosides **4** and **5** in a combined yield of 80–90%.[5,6] The ratio of the β-D-ribo (**4**) and α-L-lyxo (**5**) isomers varied between 3:2 and 1:9 depending upon the solvent, temperature, and rate of addition of iodine. Slow addition of solid iodine to a dilute solution of **3** in nitromethane at 0–10° gave good results. Separation of **4** and **5** was achieved by chromatography on a column of silicic acid using 2.5% acetone in chloroform and preparative tlc using 4% acetone in chloroform.



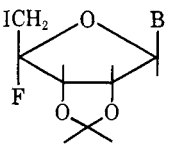
1a, R = H
b, R = SO_2Me



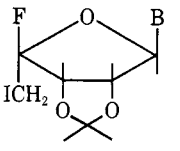
2



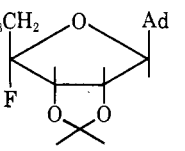
3



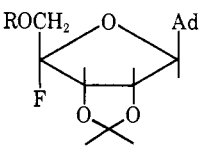
4a, B = N^1,N^6-Bz_2adenine
b, B = adenine



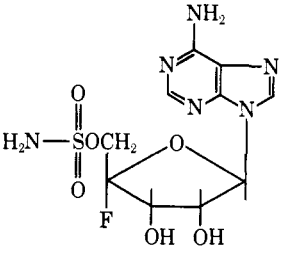
5a, B = N^1,N^6-Bz_2adenine
b, B = adenine



6



7a, R = H
b, R = $SnBu_3$
c, R = SO_2NH_2



8

The more polar β-D isomer (**4a**) was a homogeneous foam: $\lambda_{max}^{dioxane}$ 249 (ε 21,600), 275 nm (ε 17,000); ORD (dioxane) positive Cotton effect with $[\Phi]_{280}^{pk}$ +9700°, $[\Phi]_{248}$ 0°; $[\Phi]_{235}^{tr}$ −9800°; nmr $CDCl_3$ 5.41 (q, 1, $J_{2',3'}$ = 7 Hz, $J_{3'F}$ = 12 Hz, $C_{3'}H$), 6.35 (br s, 1, $J_{1',2'} \simeq$ 1 Hz, $C_{1'}H$), 8.15 and 8.67 ppm (s, 1, C_2H and C_8H). The less polar α-L-lyxo isomer **5a** was also a foam: $\lambda_{max}^{dioxane}$ 249 (ε 22,500), 275 nm (ε 17,900); nmr ($CDCl_3$) 5.08 (t, 1, $J_{2',3'}$ = $J_{3',F}$ = 5.5 Hz, $C_{3'}H$), 6.48 (q, 1, $J_{1',2'}$ = 0.5 Hz, $J_{1',F}$ = 2.5 Hz, $C_{1'}H$), 8.24 (br s, $W_{1/2}$ = 2 Hz, C_8H), 8.70 ppm (s, 1, C_2H). It is to be noted that the D-ribo isomer **4a** shows a larger $C_{3',F}$ coupling (trans) than does **5a** and that **5a** (but not **4a**) shows long-range coupling of the 4′-fluorine to both $C_{1'}H$ and one of the adenine ring protons (probably C_8H).[7] Confirmation of the structure of **4a** came from

(1) (a) E. J. Backus, H, D. Tresner, and T. H. Campbell, *Antibiot. Chemother.*, 7, 532 (1957); (b) S. O. Thomas, V. L. Singleton, J. A. Lowery, R. N. Sharpe, M. Pruess, J. N. Porter, J. H. Mowat, and N. Bohonos, *Antibiot. Ann.*, 716 (1956–1957).

(2) G. O. Morton, J. E. Lancaster, G. E. VanLear, W. Fulmor, and W. E. Meyer, *J. Amer. Chem. Soc.*, **91**, 1535 (1969).

(3) S. Chladek and J. Smrt, *Collect. Czech. Chem. Commun.*, **29**, 214 (1964).

(4) All new compounds gave satisfactory elemental analyses and nmr spectra.

(5) Addition of iodine monofluoride to glycals is known to lead to glycosyl fluorides: see, *e.g.*, L. D. Hall and J. F. Manville, *Chem. Commun.*, 35 (1968).

(6) Satisfactory addition of iodine fluoride to **2** was also achieved, but in this case separation of the isomeric products was difficult.

(7) The nmr spectra of these compounds will be considered in detail in a later paper.

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.

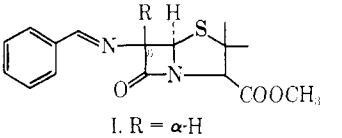
I. D. Jenkins,[11] J. P. H. Verheyden, J. G. Moffatt*
Contribution No. 90
Institute of Molecular Biology, Syntex Research
Palo Alto, California 94304
Received June 17, 1971

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).