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STUDIES ON PHOSPHONIC ACID ANTIBIOTICS. II. SYNTHESIS OF 3-(N-ACETYL-N-HYDROXYAMINO)-2(R)-HYDROXYPROPYLPHOSPHONIC ACID (FR-33289) AND 3-(N-FORMYL-N-HYDROXYAMINO)-1-TRANS-PROPENYLPHOSPHONIC ACID (FR-32863)

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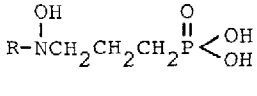
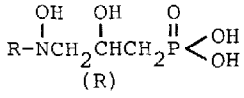
Summary: The syntheses of FR-33289 (3), originally isolated from a microorganism, and FR-32863 (6), first designed on the basis of a biogenetic consideration and recently found to be also present in nature, are described.

Recently, phosphonic acid antibiotics, e.g. fosfomycin, have attracted an increasing interest because of their unique antimicrobial activity. In the preceding paper of this series[1], we reported the syntheses of 3-(N-acetyl-N-hydroxyamino)propylphosphonic acid (FR-900098, 1), originally isolated from a microorganism source[2], and its N-formyl analogue (FR-31564, 2). The latter compound possesses a superior and clinically useful antibacterial activity and was later found to be also present in nature[3a]. In a further screening for other congeners, 3-(N-acetyl-N-hydroxyamino)-2(R)-hydroxypropylphosphonic acid (FR-33289, 3) has been recently isolated from a Streptomyces[3a]. In this communication, we wish to report the syntheses of this antibiotic and its N-formyl analogue (4), as well as the syntheses of N-acyl derivatives of 3-(N-hydroxyamino)-1-trans-propenylphosphonic acid, whose skeleton has been designed on the basis of a biogenetic consider-



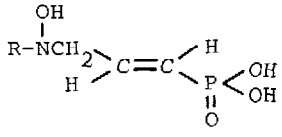
1 R=$COCH_3$

2 R=CHO



3 R=$COCH_3$

4 R=CHO

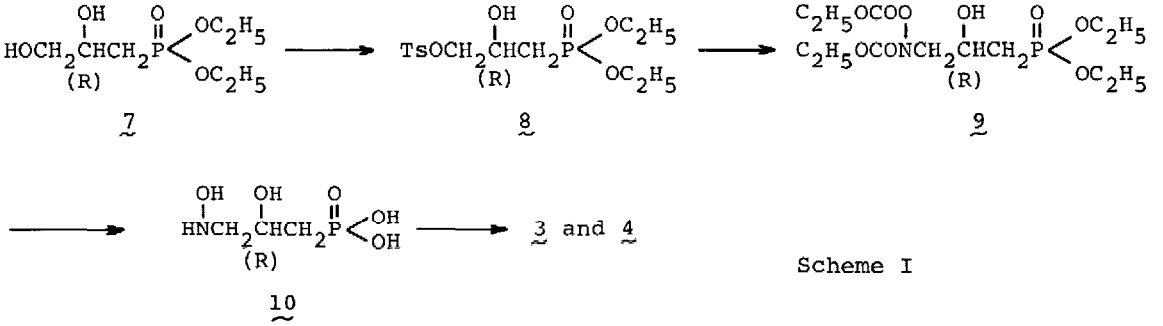


5 R=$COCH_3$

6 R=CHO

ation and very recently isolated also from a microorganism as the N-formyl derivative (FR-32863, 6)[3a].

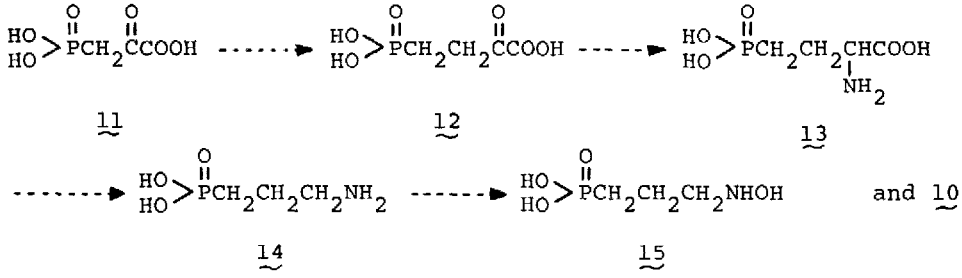
The structure of antibiotic FR-33289 was deduced, except the configuration of C-2, to be 3 on the basis of the ^{1}H NMR (D_2O) analysis [δ 1.88 (2H, dd, J=6, 18 Hz), 2.12 (3H, s), 3.78 (2H, m), 4.30 (1H, m)] and the positive color reactions ($FeCl_3$ and phosphomolybdate reagents)[3b].



Scheme I

For confirmation of this structure, FR-33289 was synthesized, as follows, starting from diethyl 2(R), 3-dihydroxypropylphosphonate (7)[4]. Tosylation of 7 with TsCl (1.0 eq. mole) in pyridine (5°C, 4 days) gave monotosylate 8 (oil, 83%), which was treated with bis(trimethylsilyl)acetamide (5°C, 30 min) and then reacted with potassium N,O-dicarboethoxyhydroxamide[5] (DMF, 70°C, 10 hr) to give 41% yield of the condensation product 9 (oil, after purification by silica-gel chromatography). Removal of the phosphonic acid protective group of 9 with trimethylsilyl bromide[6] (CH_2Cl_2, 5°C → room temp, 2 hr), followed by hydrolysis of the carboethoxy groups with 1N HCl (refl, 16 hr), gave in 47 % yield hydroxylamine 10 [mp. 138 ~ 140°(dec), $[\alpha]_D$ + 34°(c=0.2, H_2O)], which was identical with the sample derived from the natural product by hydrolysis with 1N HCl[3b], establishing the C-2 configuration to be R[7]. The final acetylation of 10 with acetic anhydride (room temp, 1 hr) gave 3 (mono Na salt, powder). This synthetic product was identified with the naturally occurring material by the physical and biological properties comparison. The formyl analogue (4) was also prepared by formylation of 10. Thus, 10 was acylated with acetic-formic anhydride (room temp, 30 min) to give FR-33699 (4, mono Na salt, powder), which showed a somewhat superior anti-

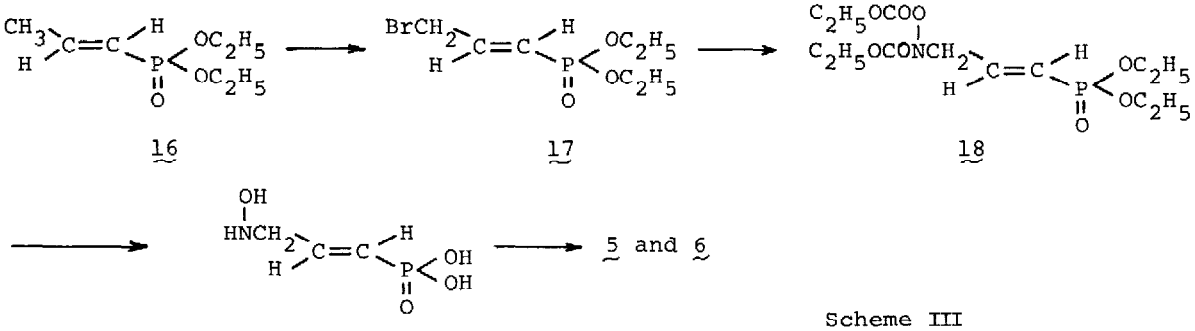
microbial activity[8] as compared with the parent antibiotic (3).



Scheme II

As pointed out in the preceding paper of this series[1], we speculated that the origin of this class of antibiotics is 3-phosphonopyruvic acid (11)[9], from which 3-aminopropylphosphonic acid (14) would be constructed via an analogous pathway to the normal TCA cycle[10], followed by transamination and decarboxylation[11], as shown in Scheme II. The intermediate 14 would then be metabolized to 15 and 10

On the basis of this hypothesis, we anticipated that some other congeners might occur in nature and were especially interested in derivatives bearing a propene skeleton which might be a further metabolite of 10 or an intermediate in transformation of the precursor 14 to 10. Thus, we prepared the acyl derivatives of 3-(N-hydroxyamino)-1-propenylphosphonic acid (19) as follows. Allylic bromination of diethyl 1-trans-propenylphosphonate (16)[12] [NBS/$(PhCO_2)_2$/CCl_4, ref1, 1.5 hr] gave in 64 % yield bromide 17 (oil), which was then reacted with potassium N,O-dicarboethoxyhydroxamide (DMF, -25 → 5°C, 2 hr) to give the condensation product 18 (oil) in 83 % yield. Removal of the protective groups of the phosphonic



Scheme III

acid and hydroxylamine functions, according to the procedure described above for preparing 10, gave 19 [mp. 127-9°(dec)] in 50 % yield. Acylation of 19 with acetic anhydride (room temp, 1 hr) and acetic-formic anhydride (room temp, 30 min) gave FR-33693 (5, mono K salt, powder, 77 % yield) and FR-32863 [6, mono K salt, mp. 178-180°(dec), 59 % yield], respectively. Interestingly, the latter compound has been very recently ascertained to be present also in the culture broth of a Streptomyces[3a]. The MIC of the latter[3a] was somewhat better than that of the former[8].

References and Notes

1. T. Kamiya, K. Hemmi, H. Takeno, and M. Hashimoto, Tetrahedron Lett., in press.
2. M. Okuhara, Y. Kuroda, T. Goto, M. Okamoto, H. Terano, E. Iguchi, M. Kohsaka, H. Aoki, and H. Imanaka, J. Antibiot., submitted for publication.
3. (a) M. Okuhara, Y. Kuroda, T. Goto, M. Okamoto, H. Terano, M. Kohsaka, H. Aoki, and H. Imanaka, J. Antibiot., submitted for publication; (b) Y. Kuroda, M. Okuhara, T. Goto, M. Okamoto, H. Terano, M. Kohsaka, H. Aoki, and H. Imanaka, J. Antibiot., submitted for publication.
4. E. Boer and H. Bosu, Can.J. Biochem., 47, 955 (1969).
5. This reagent was prepared by acylation of NH_2OH with ethyl chloroformate (2.0 eq. mole) and isolated as the potassium salt [mp. 170-171°(dec)]: this will be reported in the following paper of this series.
6. C.E. Mckenna, M.T. Higa, N.H. Cheung, and M.C. Mckenna, Tetrahedron Lett., 155 (1977).
7. For the $[\alpha]_D$ value of the product 10 derived from the natural material, see ref. 3b.
8. The MIC data of 4 and 5 will be reported elsewhere.
9. See, e.g. M. Horiguchi and H. Rosenberg, Biochem. Biophys. Acta., 404, 333 (1975), and references cited therein.
10. For metabolites formed from intermediates of the TCA cycle in microorganisms, see e.g. W.B. Turner, "Fungal Metabolites", Academic Press, 1971, pp 280-294.
11. For the amino-acid biosynthesis in microorganisms, see e.g. ibid., pp 297-300.
12. L. Horner, I. Ertel, H.-D. Ruprecht and O. Belovsky, Chem. Ber., 103, 1582 (1970).

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