

C-NUCLEOSIDES AND RELATED COMPOUNDS X
SYNTHESIS OF THE CARBOCYCLIC ANALOGUES OF
D,L-PYRAZOFURIN A (PYRAZOMYCIN) AND SHOWDOMYCIN

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Pyrazofurin A (VIII) and showdomycin (IV) are nucleosides having marked antiviral, antibacterial and antitumor activity², and their syntheses have been reported^{3,4}. We should like to describe the synthesis of their carbocyclic analogues IX and V.

The readily available olefin ester I⁵ was ozonolyzed in methylene chloride at -78°. Dimethylsulfide reduction⁶, followed by reduction with two-fold excess of tri-*t*-butoxyaluminum hydride in tetrahydrofuran gave diol ester II⁵ in 60 ~ 65% yield, based on I. Pivaloylation with 1.1 eq of pivaloyl chloride in pyridine/methylene chloride gave the monopivalate IIb in 80% yield as an oil. Similarly, the *t*-butyldimethyl silyl ether IIa could be formed in 80% yield by the addition of 1.1 eq of *t*-butyl-dimethyl silyl chloride, 2.5 eq of imidazole in dimethylformamide at 20° for 24 hrs.⁷

Oxidation of the silyl ether with ruthenium dioxide/sodium periodate/sodium bicarbonate between pH 6 and 7 in carbon tetrachloride/water⁸ gave the ketoester III⁹ in 92% yield as an oil. Treatment of the ketoester III with carbamoyl-methylene - triphenylphosphorane¹⁰ in chloroform at 20° for 4 hrs. gave VI, m.p. 64-65°, in 76% yield. Hydrolysis of VI with 50% aqueous trifluoroacetic acid at 20° for 20 mins. gave V¹¹, m.p. 171-172°, in 80% yield.

Treatment of the ketoester III with ethyl hydrazinoacetate hydrochloride and sodium acetate in methanol/water at 20° for 18 hrs. gave the hydrazone VII in 84% yield as a mixture of geometric isomers. Cyclization with refluxing 4 eq of sodium methoxide in methanol for 2 hrs. gave XI¹², m.p. 153-154° in 40% yield, after purification on silicagel plates using diethylether and chloroform (5:1) as an eluent.

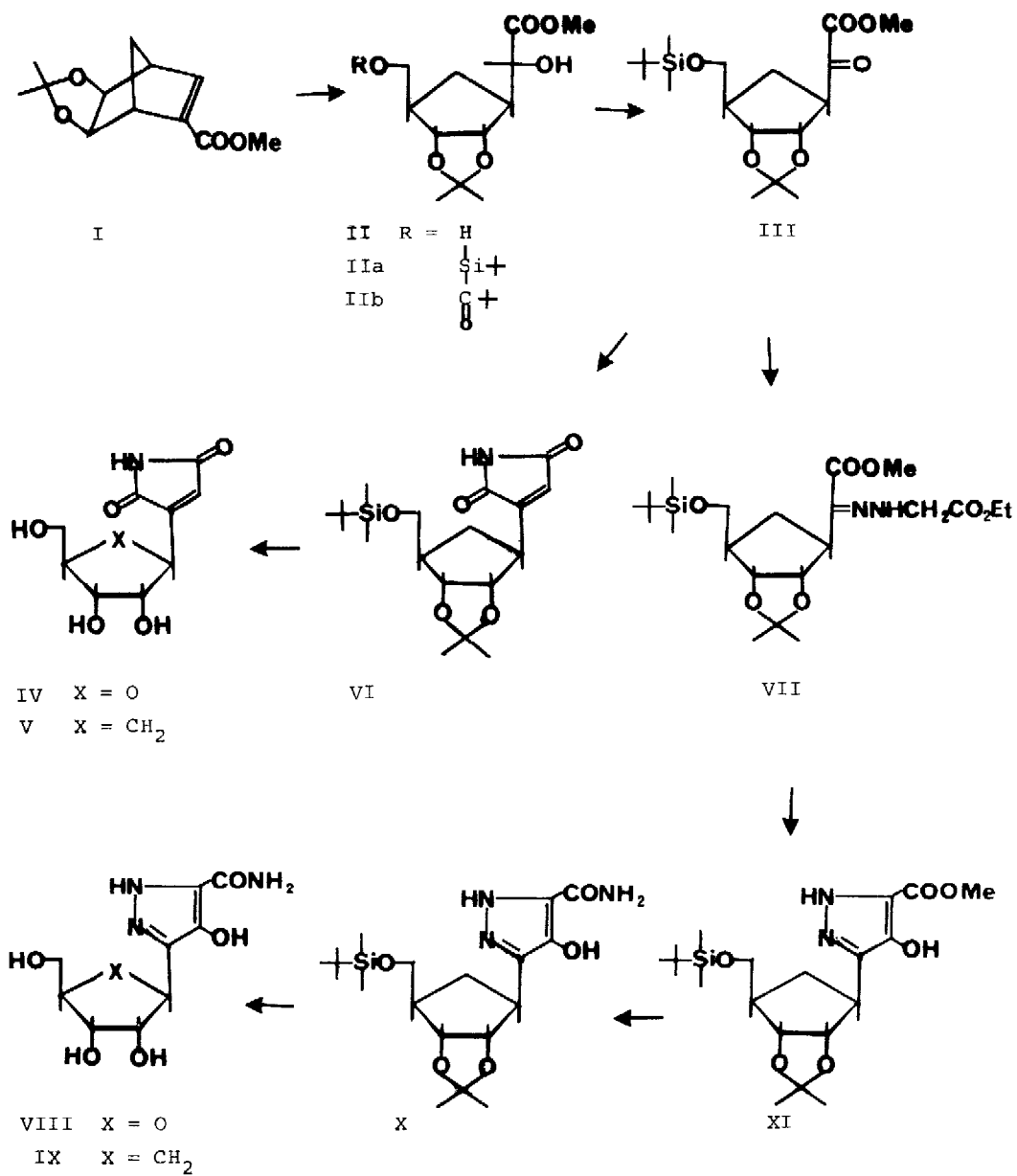
Treatment of XI with an excess of ammonia in methanol at 20° for a week gave 85% of the amide X, as a colorless foam. Hydrolysis with 50% aqueous trifluoroacetic acid for 20 minutes gave IX¹³, m.p. 216°-218°, in 80% yield.

Biological Tests

Preliminary evaluation of the carbocyclic analogues of showdomycin and pyrazofurin failed to show any activity against 15 strains of bacteria and four strains of fungi up to levels as high as 256 mcg/ml. Nine viral strains, including both DNA and RNA types, were not significantly affected by these drugs in tissue culture. In a special plaque reduction assay against a vaccinia virus challenge, slight activity was noted, but only at levels substantially higher than those required for pyrazofurin to exhibit an equivalent effect.

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References and Footnotes

1. Abstracted from part of the Ph.D. thesis of Sunggak Kim, to be submitted.
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(b) G. Trummlitz and J.G. Moffat, *J. Org. Chem.* **38**, 1841 (1973).
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9. Nmr δ (CDCl₃) 0.05(6H, s), 0.87(9H, s), 1.30(3H, s), 1.46(3H, s), 1.48 ~ 2.78 (4H, m), 3.50(2H, q, $J_{AB} = 4$ Hz), 3.83(3H, s), 4.40(1H, d.d, $J = 6$ Hz, 4Hz), 4.70 ~ 4.90(1H, m). Ir (neat) 1780, 1755 cm⁻¹, Mass (70 eV) m/e 372 (M⁺), Anal. Found for C₁₈H₃₂O₆Si: C, 57.78; H, 8.86.
10. S. Trippett and D.M. Walker, *J. Chem. Soc.*, 3874 (1959).
11. Ir (KBr) 1775, 1730, 1630 cm⁻¹, U.V.: λ_{max}^{MeOH} 228 nm (ϵ 8400), Mass(70 eV) m/e 227(M⁺), Anal. Found for C₁₀H₁₃O₅N: C, 53.08; H, 5.54; N, 6.45.
12. Nmr δ (CDCl₃) 0.05 (6H, s), 0.90(9H, s), 1.30(3H, s), 1.47(3H, s), 1.90 ~ 2.45(3H, m), 3.0 ~ 3.50(1H, m), 3.62(2H, d, $J = 2.5$ Hz), 3.90(3H, s), 4.25 ~ 4.90(2H, m), 8.80 ~ 9.25(2H, broad), Ir (KBr) 3420, 1715, 1580 cm⁻¹, U.V. λ_{max} in 0.1N HCl 230 nm (ϵ 7100) and 274 nm (ϵ 5000) λ_{max} in 0.1N NaOH 240 nm (ϵ 6300) and 320 nm (ϵ 8500) Mass (70 eV) m/e 426 (M⁺), Anal. Found for C₂₀H₃₄N₂O₆Si: C, 56.59; H, 7.69; N, 6.71.
13. Ir (KBr) 3450, 3000 ~ 3400, 1680, 1630, 1540 cm⁻¹, U.V. λ_{max} in 0.1N HCl 226 nm (ϵ 6400) and 270 nm (ϵ 4300), λ_{max} in 0.1N NaOH 235 nm (ϵ 5100) and 311 nm (ϵ 8600), mass(70 eV) m/e 257(M⁺), Anal. Found for C₁₀H₁₅N₃O₅: C, 47.09; H, 6.01; N, 16.14.