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A FACILE TOTAL SYNTHESIS OF OXANOSINE, A NOVEL NUCLEOSIDE ANTIBIOTIC

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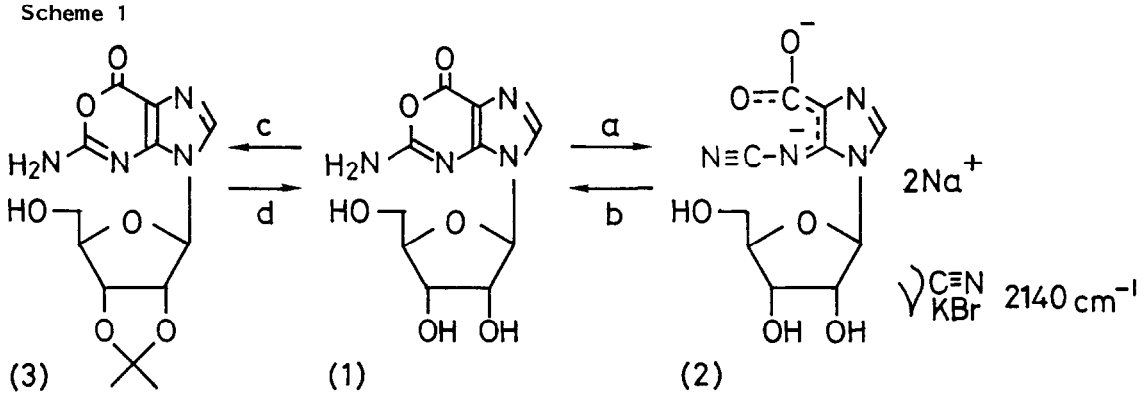
Summary: The total synthesis of oxanosine, a novel nucleoside antibiotic, has been achieved for the first time.

Oxanosine (1) is a novel nucleoside antibiotic isolated from the culture filtrate of Streptomyces capreolus MG265-CF3.[1] The structure was determined to be 5-amino-3-β-D-ribofuranosyl-3H-imidazo[4,5-d][1,3]oxazin-7-one by X-ray crystallographic analysis.[2] Intrigued by the presence of the novel heterocyclic ring system, we embarked in the total synthesis of (1). In this communication, a facile total synthesis of (1) is reported.

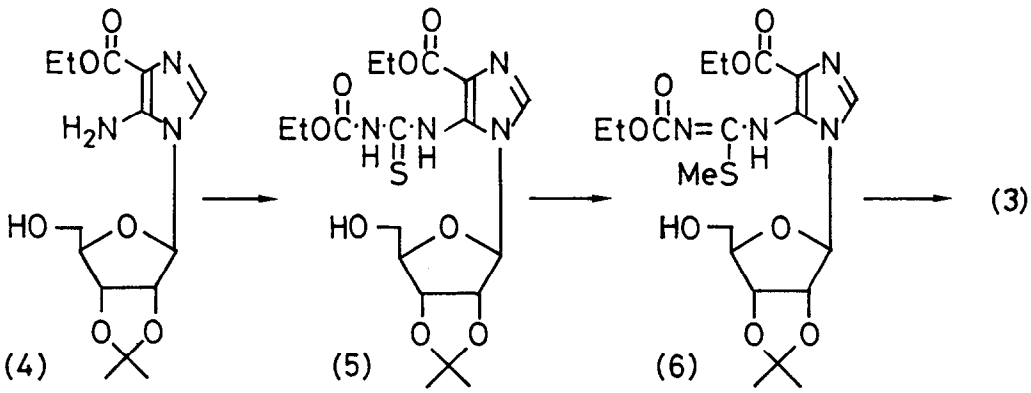
We observed that treatment of (1) with 2 equivalent amount of NaOH afforded cyanamide (2), which was recyclized to yield (1) by neutralization (Scheme 1).[3]

Scheme 1



a) 2 eq. NaOH, lyophilization
b) aq. HCl, neutralization
c) Acetone, $HC(OEt)_3$, HCl, DMF, r.t., overnight
d) 10% CH_3COOH, reflux, 1.5 hr

Scheme 2



Logical retrosynthetic analysis suggests that cyanation of amino ester (4) followed by alkaline hydrolysis and concomitant neutralization gives the desired product.

Although the attempts to effect the direct cyanation of (4) with cyanogen bromide were unsuccessful,[4] the desired transformation was achieved by the following three step reactions (Scheme 2).

Treatment of (4)[5] with EtOCON=C=S (1.1 eq., in DMF, r.t., overnight) gave thiourea (5)[6] (82%) as the sole product [mp. 96-99°; λ_{max}^{MeOH} 289 nm (log ε 4.24), 248 (4.62), 212 (4.67); $\nu_{KBr}^{C=O}$ 1710 cm^{-1}; High resolution EIMS m/z 458.1497, Calcd. for $C_{18}H_{26}N_4O_8S$ 458.1470]. Methylation of (5) with CH_3I (1.5 eq., in 0.1N NaOH, r.t., overnight) gave the S-methylisothiourea (6)[6] (55%) [mp. 65-68°; λ_{max}^{MeOH} 267 (4.27), 253 (4.26), 212 (4.41); $\nu_{KBr}^{C=O}$ 1750 cm^{-1}; HREIMS m/z 472.1625, Calcd. for $C_{19}H_{28}N_4O_8S$ 472.1625]. Treatment of (6) with 10 equivalents of NaOH (0.2N aq., reflux 30 min) followed by neutralization with 0.1N-HCl furnished the desired imidazo-oxazinone (3) (19%).[7] The synthetic (3) displays IR, ^{1}H-NMR and mass spectra identical with those of the natural one, which was almost quantitatively transformed to oxanosine (Scheme 1). Thus, the total synthesis of oxanosine has been established.

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References and Notes

1. N. Shimada, N. Yagisawa, H. Naganawa, T. Takita, M. Hamada, T. Takeuchi and H. Umezawa, J. Antibiot., 34, 1216 (1981)
2. H. Nakamura, N. Yagisawa, N. Shimada, T. Takita, H. Umezawa and Y. Iitaka, J. Antibiot., 34, 1219 (1981)
3. Unpublished results
4. N. J. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg and G. Shaw, J. Chem. Soc., Perkin I, 1973, 1720
5. A. Yamazaki and M. Okutsu, J. Heterocyclic Chem., 15, 353 (1978)
6. The ^{1}H-NMR spectrum is in agreement with the assigned structure.
7. The low yield may be due to instability of intermediary 2',3'-O-isopropylidene-(2).

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