Tetrahedron Letters Vol. 21, pp 3613 - 3616 0040-4039/80/0908-3613$02.00/0

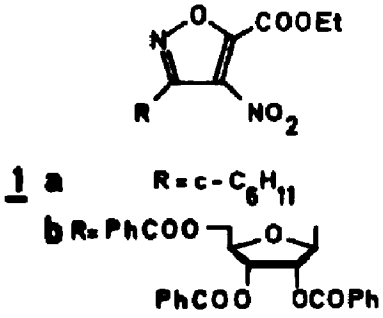
A PATHWAY TO 3-(β-D-RIBOFURANOSYL)-4-NITRO-5-ETHOXYCARBONYL-ISOXAZOLES, USEFUL IN THE SYNTHESIS OF PYRAZOFURIN ANALOGUES

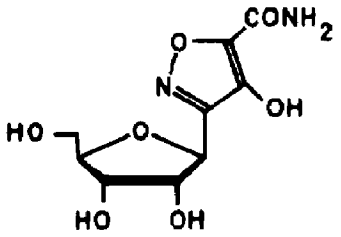
J.A. Deceuninck, D.K. Buffel, G.J. Hoornaert*

Department of Chemistry, KULeuven, Celestijnenlaan 200 F, 3030 Heverlee, Belgium

The synthesis of 3-cyclohexyl and 3-β-D-ribofuranosyl-4-nitro-5-ethoxycarbonyl isoxazole, is realized by conversion of cyclohexane carboxaldehyde and 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allose into the corresponding nitromethyloximes followed by reaction with ethylchlorooxoacetate.

The occurence in nature of a number of C-glycosyl nucleosides, many of which show antiviral or antitumoral activity, has stimulated a lot of research on this type of compounds[1].
In this we would like to communicate an easy route towards compounds of type 1, which has been developed in the course of our study on these nucleoside antibiotics.
The compound 1b is useful in the synthesis of isoxazole analogues of pyrazofurin 2, which has established cytotoxic activity[2].





2

There are few methods yielding substituted isoxazoles of type 1. The most convenient one appeared to be a 1,3-dipolar cycloaddition of a (benzoyl protected) ribofuranosylnitrile-oxide[3] with the activated olefins 3 and 4, but this route was unsuccessful in our hands.

3 4

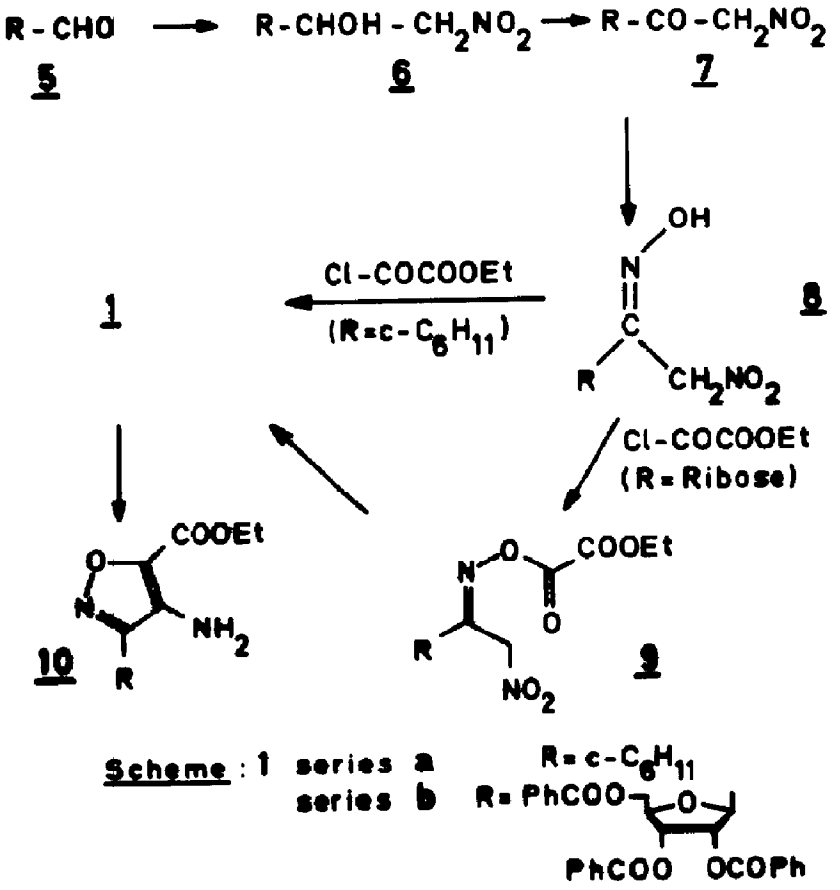
To test a new concept based on the synthesis and cyclization of an acylated nitroxime of type 9, we initially examined a model system using (commercially available) cyclohexane carboxaldehyde 5

This aldehyde underwent facile reaction with nitromethane in the presence of sodium methoxide, giving the nitroalcohol 6a. The nitroketone 7a was obtained by oxidation of 6a (0.87 g, 5 mmo with Jones reagent (6 mL) in acetone (20 mL) at room temperature. The reaction mixture was wo ked up and purified by rapid chromatography on a silica column (benzene-ethyl acetate 6:1)(80% yield). A solution of 7a (0.69 g, 4 mmol) and hydroxylamine sulphate (0.13 g, 8 mmol) in a mi ture benzene-ethanol (40 mL, 1:1) was refluxed for 4 hours. The product was worked up in the usual way to give the oxime 8a, (0.62 g, 90% yield). On treatment of 8a (3.5 mmol) with ethyl chloro oxoacetate (0.48 g, 3.5 mmol) in 20 mL diethylether at room temperature, followed by ch matography on a silica column (benzene-ethylacetate 8-1) the isoxazole 1a could be isolated in 70% yield. It showed following characteristics.

H-NMR spectrum ($CDCl_3$, 100 MHz, δ in ppm) : 1.44(t,3,$OCH_2\underline{CH_3}$), 4.52(q,2,$O\underline{CH_2}CH_3$). Mass spectr (m/e) : 267 : M^+-H; IR ($CHCl_3$, cm^{-1}) $\nu(NO_2)$: 1530, 1320; $\nu(C=O)$: 1755.

The reduction of 1a is realised on treatment with Al-amalgam[5] in diethyl ether at 0°C, giving amino-isoxazole 10a in 50% yield.

H-NMR spectrum ($CDCl_3$, 100 MHz, δ in ppm) : 1.46(t,3,$OCH_2\underline{CH_3}$), 4.28(br.s,2,NH_2), 4.42(q,2,$O\underline{CH_2}$ CH_3). Mass spectrum (m/e) : M^+ : 328. IR ($CHCl_3$, cm^{-1}) : $\nu_{(NH_2)}$: 3500-3300, 1580; $\nu_{(C=O)}$: 1720.



Scheme : 1 series a R = c-C_6H_{11}
series b R = PhCOO-

The same procedure could be applied for the synthesis of the nitro substituted alcohol[6] 6b, nitro-ketone 7b, and oxime 8b. However, when 8b was subjected to the same reaction conditions as 8a, no trace of 1b was detected, even at higher temperatures. The NMR spectrum of the reaction product, after evaporation, showed the conversion of the oximino group into the acyl derivative 9. Only by treatment with 2 equivalents of pyridine in 2-methyl-2-butanol, did the reaction take place to yield the nitro isoxazole 1b in 33% yield.

Therefore a solution of 8b (4 g, 7.3 mmol) in a mixture of 2-methyl-2-butanol (750 mL) and pyridine (1.15 g, 14.6 mmol), was treated with ethyl chlorooxoacetate (1.1 g, 8 mmol) at room temperature for 4 hours. After evaporation the obtained mixture was purified by chromatography on a silica column (benzene-ethyl acetate 9:1), yielding compound 1b which showed following spectral features.

H NMR spectrum ($CDCl_3$, 100 MHz, δ in ppm) : 1.40(t,3,$OCH_2\underline{CH_3}$), 4.50(q,2,$O\underline{CH_2}CH_3$), 4.52-4.92(m, 3,C_4,H,C_5,H_2), 5.70(d,1,C_1, $J_{1',2'}$= 5 Hz), 5.91(t,1,C_3,H, $J_{3',4'}$= 5 Hz), 6.20(t,1,C_2,H, $J_{2',3'}$= 5 Hz). Mass spectrum (m/e) : M^+ : 630. IR ($CHCl_3$, cm^{-1}) : $\nu_{(NO_2)}$: 1545, 1320; $\nu_{(COOEt)}$: 1755. The substitution pattern of products 1a and b could be proved by ^{13}C-NMR, since the obtained chemical shifts of the C_4 and C_5 ring-atoms correlate best to the theoretical ones[7a,b] calculated for a nitro-substituent at C_4 and an ethoxy carbonyl at C_5 (cfr table).

Table : ^{13}C chemical shifts (ppm downfield from TMS) of substituted isoxazoles

	expected				measured	
	substituent		substituent		1a	1b
C_4	NO_2	130-140	COOEt	100-110	133.0	132.5
C_5	COOEt	150-160	NO_2	180-190	157.4	157.6

The amino isoxazole 10b is obtained in the same way as 10a.

H NMR spectrum ($CDCl_3$, 100 MHz, δ in ppm) : 1.36(t,3,$OCH_2\underline{CH_3}$), 4.35(q,2,$O\underline{CH_2}CH_3$), 4.52-4.92(m, 5,C_4,H, C_5,H_2, NH_2), 5.54(d,1,C_1,H, $J_{1',2'}$= 6 Hz), 5.88(t,1,C_3,H, $J_{3',4'}$= 5.5 Hz), 6.03(t,1,C_2,H, $J_{2',3'}$= 6 Hz).

Mass spectrum (m/e) : M^+ : 600. IR($CHCl_3$,cm^{-1}) $\nu_{(NH_2)}$: 3500-3300, 1585.

The configuration of these products has not yet been established, but the β-structure is favoured as we have never observed formation of anomeric pairs in the course of these investigations. Further experiments concerning the extension of this method and the synthesis of the isoxazole analogues of pyrazofurine and the formycins are in progress.

Acknowledgements

The authors wish to thank the "FKFO" for financial support. They are indebted to the "IWONL" (JD and DB) and the "NFWO" (DB) for a grant. They also wish to thank S. Toppet for C NMR analyses and R. De Boer and P. Valvekens for technical assistance.

References

1. S. Hanessian, A. Pernet, Adv.Carbohydr.Chem.(Biochem.), 33, 111 (1976)
2. R. Suhaldolnik, "Nucleosides as biological probes", Wiley Interscience 1979, p.281
3. H. Albrecht, D. Repke, J. Moffatt, J.Org.Chem., 40, 2143(1975)
4. "Selection of oxidants in synthesis : oxidation at the carbon atom", L.J. Chinn, Marcel Dekker, Inc., New York (1971), p.42
5. G. Morgan, H. Burgess, J.Chem.Soc., 697 (1921)
6. J. Repke, H. Albrecht, J. Moffatt, J.Org.Chem., 40, 2481 (1975)
7. (a) J. Gainier, G. Howarth, W. Hoyle, Org.Magn.Res., 8, 226 (1976)
   (b) R. Wasylishen, T. Clem, E. Becker, Can.J.Chem., 53, 596 (1975)

(Received in UK 9 July 1980)