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REACTION OF α,β-UNSATURATED SUGAR LACTONES WITH FORMALDOXIME

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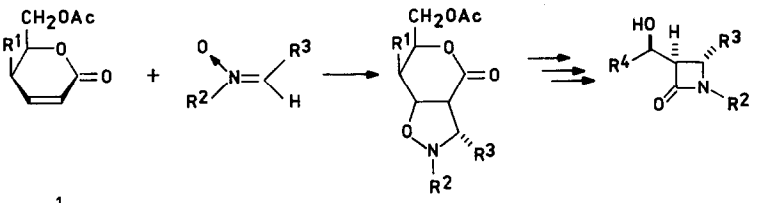
Abstract - Unsaturated sugar δ-lactones react with a mixture of hydroxylamine and formaldehyde (formaldoxime) either *via* stepwise process to produce the 1-aza-3,9-dioxa-8-oxo-bicyclo(4.3.0)nonan derivative, or *via* 1,3-dipolar cycloaddition of the nitrone form affording the 8-aza-3,7-dioxa-2-oxo-bicyclo-(4.3.0)nonan derivative.

In previous papers, we have reported that 1,3-dipolar cycloaddition of nitrones to α,β-unsaturated sugar lactones proceeded regiospecifically to afford a mixture of stereoisomers.[1,2] The nitrone molecule approaches the lactone ring anti to the terminal acetoxymethyl group of the substrate, and *exo* addition is favoured over *endo* addition. Adducts having the isoxazolidine ring fused to the sugar unit have been used as precursors of enantiomerically pure trisubstituted azetidinones-2 (Scheme 1).[3] The full sequence of reactions leading from the lactone to the β-lactam skeleton, which is based on a previously published approach,[4] have been successfully performed for the nitrones derived from anisaldehyde and *N*-phenylhydroxylamine.[2,3]

Scheme 1



1 : R^1=H

2 : R^1=OAc

R^2=Aryl, Alkyl, Benzyl ; R^3=Aryl, Alkyl, CO_2Bu ; R^4=polyol chain

The present work directs attention to the simplest nitrone which is the tautomeric form of formaldoxime. It is known that, under certain conditions, formaldoxime can react directly with olefins in a 1,3-dipolar fashion to produce isoxazolidines.[5,6] As dipolarophiles we selected racemic 6-acetoxymethyl-5,6-dihydropyron-2 (1) and 4,6-di-*O*-acetyl-2,3-dideoxy-D-threohex-2-enoaldono-1,5-lactone (2).

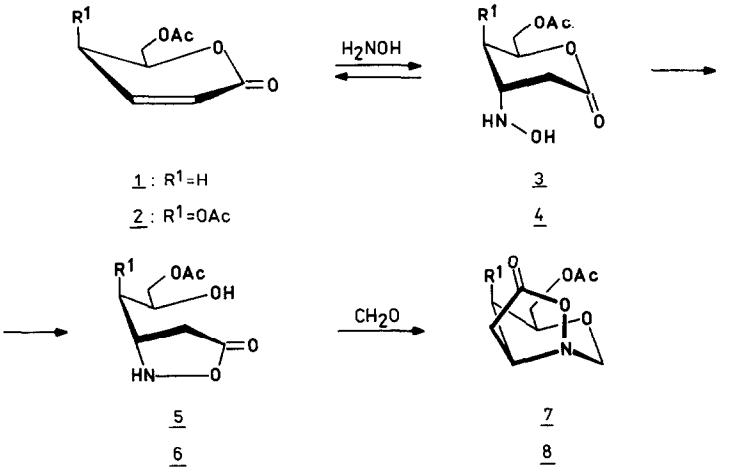
RESULTS AND DISCUSSION

Formaldoxime was prepared *in situ* by the reaction of formaldehyde and hydroxylamine hydrochloride in the presence of sodium hydroxide in a methanol-water solution.[5] Cycloadditions were perfor-

med according to two general procedures. The first one used a 5-fold excess of formaldoxime and the reaction mixture was storred at room temperature for 3 days. In the second, equimolar amounts of substrates were heated at 70°C for 3 h.

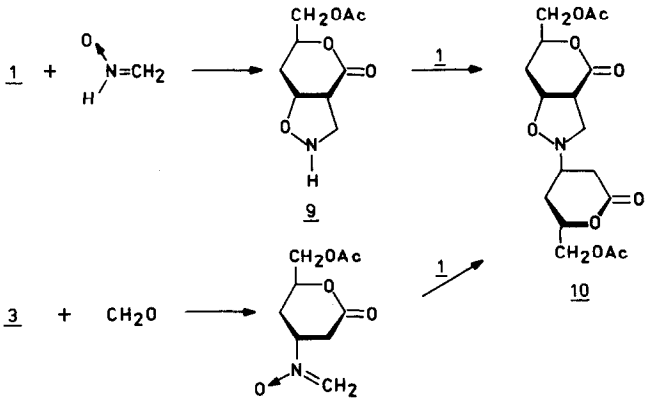
Using the first procedure, lactone 1 afforded stereospecifically the unexpected bicyclic adduct 7 in 80% yield (Scheme 2). The structure of 7 was proved unequivocally by X-ray crystallography (Fig. 1; see Experimental). It can be postulated that reaction proceeds *via* a two-step addition to 7 (Scheme 2). The first step consists in an axial approach of hydroxylamine to the double bond of 1 to afford a Michael adduct 3. Subsequently the hydroxyl group of the hydroxylamine residue opens the six-membered lactone ring to produce isoxazolidinone 5. This pathway corresponds well with that previously reported for the highly stereoselective and reversible addition of *O*-benzylhydroxylamine to lactone 1, in which the nucleophile is added *anti* with respect to the equatorial acetoxymethyl group.[7] Compound 5 adds a formaldehyde molecule producing a bicyclic system 7.

Scheme 2



Hydroxylamine does not add to the double bond of the lactone 1 when the reaction mixture is heated because the equilibrium of Michael addition is entirely shifted to substrates. On the other hand, 1,3-dipolar cycloaddition of the nitrone tautomeric form of formaldoxime to lactone 1, which is slow at room temperature, begins to play a decisive role. The cycloadduct 9, however, reacts immediately with a second molucule of lactone 1 to produce a double adduct 10.

Scheme 3



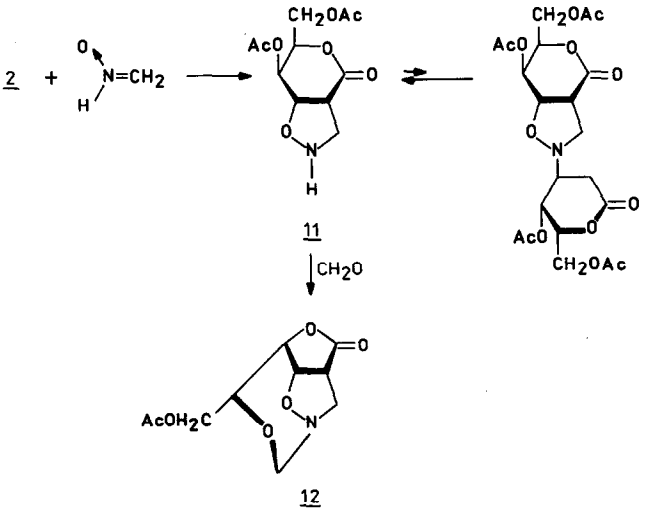
The alternative pathway for the formation of 10 should also be taken into consideration. This consists in formation of a nitrone from hydroxylamine 3 and formaldehyde at the first step of reaction. Subsequently, the nitrone affords 10 *via* 1,3-dipolar cycloaddition to lactone 1 (Scheme 3).

The structure of 10, which is a mixture of two diastereomeric racemates, was proved on the basis of analytical and spectral data. Owing to the slow inversion process at the isoxazolidine nitrogen atom,[3] 10 displays considerable line broadening in the ^{1}H-n.m.r. and ^{13}C-n.m.r. spectra taken at room temperature; at 100°C in pyridine solution 10 shows well resolved ^{1}H-n.m.r. spectrum.

In contrast to 1, lactone 2 at room temperature produces compound 8 in 20% yield only, probably due to the *syn* interaction between the acetoxy substituent and the neighbouring five-membered isoxazolidine ring. In addition to 8, the 1,3-cycloadduct 11 (40%) and its rearranged derivative 12 (10%) are formed (Scheme 4). Two-step addition to lactone 2, at first hydroxylamine and subsequently formaldehyde, increased the content of 8 up to 45%.

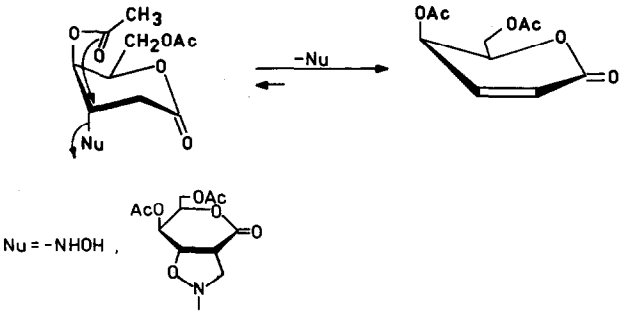
Upon heating 2 with formaldoxime, 11 becomes the only product (85%). In contrast to 9, 11 does not add the second molecule of 2. Upon prolongation of heating, 11 undergoes lactone ring contraction followed by addition of formaldehyde to afford the tricyclic structure 12.

Scheme 4



The structures of 11 and 12 were determined on the basis of their m.s., ^{1}H-n.m.r., and ^{13}C-n.m.r. data. In addition, the structure of crystalline 12 was proved by the X-ray crystallography, thus proving also the structure and configuration of the bicyclic precursor 11 (Fig. 2).

Scheme 5



The difference in reactivity between 1 and 2 is probably connected with the participation of the 4-acetoxy substituent which facilitates the retro Michael addition, causing shift if reversible reaction toward the 1:1 adduct 11 and its rearranged form 12 (Scheme 5).

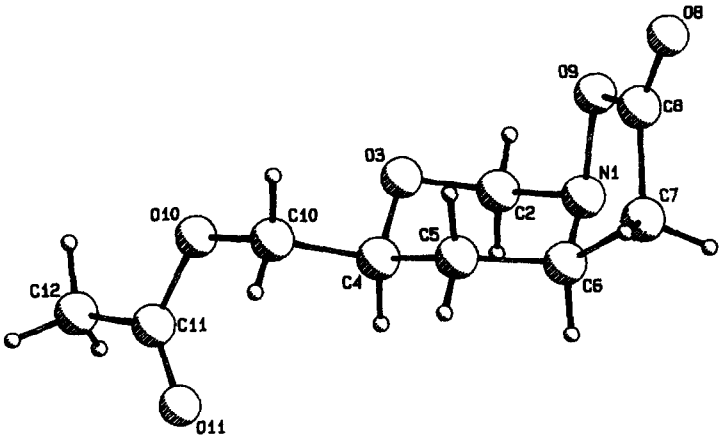


Fig.1 Computer generated perspective drawing of (4S*, 6R*) 4-acetoxymethyl-1-aza-3,9-dioxa-8-oxo-bicyclo(4.3.0)nonan (7).

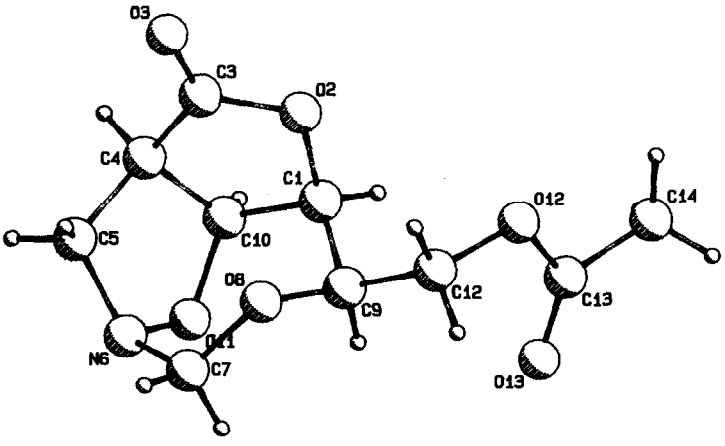


Fig. 2 Computer generated perspective drawing of (1R, 4R, 9R, 10S) 9-acetoxymethyl-6-aza-2,8,11-trioxa-3-oxo(4.3.2.$0^{4,10}$)undecan (12).

EXPERIMENTAL

^{1}H and ^{13}C-n.m.r. spectra were recorded for solutions in $CDCl_3$ on a Bruker AM-500 spectrometer (TMS=0 ppm). I.r. spectra were recorded on a Unicam SP-200 spectrophotometer. Mass spectra were recorded with a Finigan Mat 8200 mass spectrometer. Tlc was performed with Merck DC Alufolien Kieselgel 60F-254. Column chromatography was carried out with silica gel Merck (230-400 mesh). Mps are uncorrected.

Lactones 1 and 2 were obtained according to the procedure described earlier.[8]

Crystallography. - Compound 7 ($C_9H_{11}NO_5$) crystallized in monoclinic I2/a space group, a=15.257 (3), b=5.714(2), c=23.721(4) Å, β=94.44(2)°, and z=8. The structure was solved by direct method using MULTAN program system[9] and refined to R=0.051 and Rw=0.045 by using 1186 independent reflections of Mo-Kα radiation.

Compound 12 ($C_{10}H_{13}NO_6$) crystallized in monoclinic $P2_1$ space group, a=5.558(2), b=8.119(4), c=11.948(4) Å, β=98.19(3)°, and z=2. The structure was solved by direct methods using the MULTAN program system[9] and refined to R=0.046 and Rw=0.049 by using 920 independent reflections of Mo-Kα radiation.

(4S*, 6R*) 4-acetoxymethyl-1-aza-3,9-dioxa-8-oxo-bicyclo[4.3.0]nonan (7). - To a solution of hydroxylamine hydrochloride (1.0 g, 0.015 mol) and sodium hydroxide (0.58 g, 0.015 mol) in 30% aq. methanol (3 ml) below 35°C was added 37% aq. formaldehyde (1.17 g, o.o15 mol). To the solution of formaldoxime thus obtained, lactone 1 (0.5 g, 0.003 mol) was added at room temperature. The mixture was left at room temperature for 3 days. Subsequently the mixture was extracted with methylene chloride. The extract was dried and evaporated. The oily residue was purified on a silica gel column using hexane-ethyl acetate 1:1 as an eluant to afford crystalline product 7 (80%); m.p. 107-110°C, i.r. (CH_2Cl_2): 1785, 1740 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 1.55 (ddd, 1H, J_{4B}=2.4, J_{56}=5.2, $J_{55'}$=13.6 Hz, H-5), 1.67 (dt, 1H, $J_{45'}$=$J_{5'6}$=11.5 Hz, H-5'), 2.11 (s, 3H, OAc), 2.48 (d, 1H, $J_{77'}$=16.5 Hz, H-7), 3.16 (dd, 1H, $J_{67'}$=7.0 Hz, H-7'), 3.78 (m, 1H, H-4), 3.95 (m, 1H, H-6), 4.06 (dd, 1H, J_{4A}=6.4, J_{AB}=11.8 Hz, CH_AH_BOAc), 4.16 (dd, 1H, J_{4B}=3.7 Hz, CH_AH_BOAc), 4.53 (d, 1H, $J_{22'}$=13.4 Hz, H-2), 5.20 (d, 1H, H-2'); ^{13}C-n.m.r. ($CDCl_3$): 20.78 (Ac), 27.31 (C-5), 39.47 (C-7), 56.90 (C-6), 66.05 (CH_2OAc), 72.30 (C-4), 80.70 (C-2), 170.76 (Ac), 172.86 (C=O). Anal. Calcd for $C_9H_{11}NO_5$: C, 50.20; H, 6.04; N, 6.51. Found: C, 50.1; H, 6.1; N, 6.3.

(1R*, 4S*, 6R*) 4-Acetoxymethyl-8-[(6'S*, 3'R*) 6'-acetoxymethyltetrahydro-2H-pyronyl-4']-3,7-dioxa-2-oxo-bicyclo[4.3.0]nonan (10). - To a solution of formaldoxime obtained according to the procedure described above, lactone 1 (2.6 g, 0.015 mol) was added at room temperature. The mixture was heated at 70°C for 2 h and after cooling extracted with methylene chloride. The extract was dried and evaporated to give an oily substance. Chromatographical purification gave crystalline product 10 (60%); m.p. 130-133°C; i.r. (CH_2Cl_2): 1750 cm^{-1}; ^{1}H-n.m.r. (pyridine-d_5; 100°C): 1.85-2.15 (m, 4H, H-5,5a,5',5'a), 1.95 (s, 6H, 2OAc), 2.76 (dd, 1H, $J_{3'4'}$=5.5, $J_{3'3'}$=16.8 Hz, H-3'), 2.83 (dd, 1H, $J_{3'4'}$=5.2 Hz, H-3'a), 3.08(m, 1H, H-1), 3.22 (quintet, 1H, ΣJ=20.1 Hz, H-4'), 3.56 (t, 1H, ΣJ=18.6 Hz, H-9a), 3.70 (q, 1H, ΣJ=23.7 Hz, H-9b), 4.20-4.35 (m, 4H, $2CH_2OAc$), 4.49 (quintet, 1H, ΣJ=14.6 Hz, H-6), 4.89 (m, 2H, H-4,6'). MS m/z: M$^+$ 385, M-170, M-214. Anal. Calcd for $C_{17}H_{23}NO_9$: C, 52.98; H, 5.97; N, 3.63. Found: C, 52.8; H, 6.2; N, 3.5.

(4S, 5R, 6S) 5-Acetoxy-4-acetoxymethyl-1-aza-3,9-dioxa-8-oxo-bicyclo[4.3.0]nonan (8), (1R, 4S, 5R, 6S) 5-acetoxy-4-acetoxymethyl-8-aza-3,7-dioxa-2-oxo-bicyclo[4.3.0]nonan (11), and (1R, 4R, 9R, 10S) 9-acetoxymethyl-6-aza-2,8,11-trioxa-3-oxotricyclo[4.3.2.0^{1,5}]undecan (12). - To a solution of formaldoxime obtained according to the procedure described for 7, lactone 2 (0.68 g, 0.003 mol) was added at room temperature. The mixture was left at room temperature for 3 days. Subsequently the mixture was extracted with methylene chloride. The extract was dried and evaporated. The oily residue was separated on a silica gel column using hexane-ethyl acetate 1:1 mixture as an eluant to give three products and unreacted lactone (20%):

8: 20%; m.p. 106-108°C; $[\alpha]_D$ +73.0° (c 1, CH_2Cl_2); i.r. (CH_2Cl_2): 1760, 1805 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 2.06, 2.15 (2s, 6H, 2OAc), 2.45 (d, 1H, $J_{77'}$=16.5 Hz, H-7), 3.08 (dd, 1H, $J_{67'}$=7.6 Hz, H-7'), 3.96 (dt, 1H, J_{45}=1.3, J_{4A}=6.7, J_{4B}=6.1 Hz, H-4), 4.06 (dd, J_{56}=3.8 Hz, H-6), 4.09 (dd, 1H, J_{AB}=11.5 Hz, H-A), 4.14 (dd, 1H, H-B), 4.59 (d, 1H, $J_{22'}$=13.5 Hz, H-2), 5.27 (d,1H, H-2'); ^{13}C-n.m.r. ($CDCl_3$): 20.28, 20.66 (2OAc), 34.99 (C-7), 59.28 (C-6), 62.28 (C-5), 64.77 (CH_2=Ac), 73.66 (C-4), 80.67 (C-2), 170.49, 170.79 (2Ac), 172.41 (C=O); MS m/z: M$^+$ 273.0849(273.0849 for $C_{11}H_{15}NO_7$).

12; 10%; m.p. 119-121°C; $[\alpha]_D$ -122.2° (c 1, CH_2Cl_2); ^{1}H-n.m.r. ($CDCl_3$): 2.09 (s, 3H, OAc), 3.47 (d, 1H, H-5), 3.63 (m, 2H, H-4,5'), 4.1-4.3 (m, 3H, H-9, CH_2OAc), 4.43 (d, 1H, $J_{77'}$=12.4 Hz, H-7), 4.59 (d, 1H, H-7'), 4.81 (d, 1H, J_{110}=7.3 Hz, H-1), 5.26 (t, 1H, J_{410}=9.1 Hz, H-10); ^{13}C-n.m.r. ($CDCl_3$): 20.76 (Ac), 50.63 (C-4), 53.31 (C-5), 63.29 (CH_2=Ac), 78.84, 80.96, 82.09 (C-1,10,9), 88.38 (C-7), 170.48 (Ac), 174.34 (C=O); MS m/z: M$^+$ 243.0729 (243.0729 for $C_{10}H_{13}NO_6$).

11; 40%; syrup; $[\alpha]_D$ +27.4° (c 1, CH_2Cl_2); i.r. (CH_2Cl_2): 3460, 1750 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 2.10, 2.13 (2s, 6H, 2OAc), 3.23 (dd, $J_{99'}$=10.0, J_{19}=6.3 Hz, H-9), 3.58 (dd, 1H, $J_{19'}$=8.5 Hz, H-9'), 3.69 (m, 1H, J_{16}=8.1 Hz, H-1), 4.22 (dd, 1H, J_{4A}=6.7, J_{AB}=11.8 Hz, H-A), 4.27 (dd, 1H, J_{4B}=5.7 Hz, H-B), 4.45 (dd, 1H, J_{56}=3.1 Hz, H-6), 4.93 (dt, 1H, J_{45}=1.5 Hz, H-4), 5.19 (dd, 1H, H-5); ^{13}C-n.m.r. ($CDCl_3$): 20.60, 20.67 (2Ac), 45.44 (C-1), 57.06 (C-9), 61.86 (C-5), 65.2 (CH_2OAc), 73.70 (C-4), 75.22 (C-6), 168.40 (C=O), 169.24, 170.32 (2Ac); MS m/z: M$^+$ 273.0849 (273.0849 for $C_{11}H_{15}NO_7$).

(4S, 5R,6S) 5-Acetoxy-4-acetoxymethyl-1-aza-3,9-dioxa-8-oxo-bicyclo[4.3.0]nonan (8) and (1R, 4S, 5R, 6S) 5-acetoxy-4-acetoxymethyl-8-aza-3,7-dioxa-2-oxo-bicyclo[4.3.0]nonan (11). - To a solution of hydroxylamine hydrochloride (1.0 g, 0.015 mol) and sodium hydroxide (0.58 g, 0.015 mol) in 30% aq. methanol (3 ml) lactone 2 (1.0 g, 0.004 mol) was added. The mixture was allowed to stand at room temperature for 3 h, subsequently, 37% aq. formaldehyde (1.17 g) was added, and solution was left overnight. Products were extracted with dichloromethane. The extract was dried, evaporated, and separated on a silica gel to give: unreacted substrate 2 (0.2 g), 8 (0.53 g, 45%), and 11 (0.26 g, 25%).

(1R, 4S, 5R, 6S) 5-Acetoxy-4-acetoxymethyl-8-aza-3,7-dioxa-2-oxo-bicyclo(4.3.0)nonan (11). - To a solution of formaldoxime obtained according to the procedure described for 7, lactone 2 (3.4 g, 0.015 mol) was added. The mixture was heated at 70°C for 3 h. Subsequently the mixture was extracted with methylene chloride. The extract was dried evaporated and purified on a silica gel column to give 11 (85%).

ACKNOWLEDGMENTS

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