CONFIGURATION AND CONFORMATION OF THE PRODUCTS OF REACTION OF 3,4-DI-O-ACETYL-2-DEOXY-2-NITROSO-β-D-ARABINO-PYRANOSYL CHLORIDE WITH PYRAZOLE

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ABSTRACT

3,4-Di-O-acetyl-2-deoxy-2-nitroso- β -D-arabinopyranosyl chloride reacts with pyrazole in acetonitrile to afford 1-(3,4-di-O-acetyl-2-deoxy-2-hydroxyimino- α -D-erythro- and - β -D-erythro-pentopyranosyl)pyrazole, the configuration and conformation of which were established on the basis of ¹H-n.m.r., polarimetric, and crystallographic data.

INTRODUCTION

We have reported on the products of reaction of 3,4,6-tri-O-acetyl-2-deoxy-2nitroso- α -D-gluco-1 and - α -D-galacto-pyranosyl² chlorides with pyrazole and - α -Dglucopyranosyl chloride with methyl esters of some hydroxy-L- α -amino acids³. As in the reactions of these chlorides with alcohols and phenols⁴, the corresponding 3,4,6-tri-O-acetyl-2-deoxy-2-hydroxyimino-D-hexopyranosides were obtained. The interactions of the substituents are similar to those observed with 2-oxo sugars⁵ and result in deformation of the sugar ring. This deformation has been inferred from the ¹H-n.m.r. data³, as has the configuration of the 2-C=N-OH group^{4,6,7}. The unambiguous assignment of the configuration and conformation could, however, be made only on the basis of the results of crystallographic measurements.

We now report on the products of the reaction of 3,4-di-O-acetyl-2-deoxy-2nitroso- β -D-arabinopyranosyl chloride (2) with pyrazole.

RESULTS AND DISCUSSION

3,4-Di-O-acetyl-D-arabinal (1), the precursor of 2, was obtained in yields of \sim 65% by a modification of reported methods^{8,9}.

Condensation of 2 with 2 equiv. of pyrazole in acetonitrile for 48 h at room temperature gave 1-(3,4-di-O-acetyl-2-deoxy-2-hydroxyimino- β -D-erythro-(7) and $-\alpha$ -D-erythro-pentopyranosyl)pyrazoles (8) in ~70% combined yield and in the



ratio $\sim 1:1$. When the reaction was carried out at $\sim 80^{\circ}$, 7 was the sole product (65% yield). When a solution of 8 in acetonitrile containing a catalytic amount of hydrogen chloride or 2 was heated, 8 was converted into 7. When 2-propanol was added to the solution, 8 disappeared and 5 and 6 could be isolated together with small amounts of 7 (5 and 6 were also obtained by the reaction of 2 with 2-propanol). Under similar conditions, 5–7 remained unchanged. Compounds 7 and 8 were also recovered after heating solutions in acetonitrile or in the presence or absence of small amounts of such bases as pyrazole or triethylamine.

The above findings suggest that 7 and 8 are formed according to the mechanism outlined for the reaction of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -Dgalactopyranosyl chloride with pyrazole², namely, that a thermodynamic product (7) is formed by the addition of pyrazole to the reactive intermediate 3, which is similar to 4, and is a transformation product of 2 in solution^{4,10,11}. The kinetic product 8 is formed by the reaction of 4 with the more nucleophilic nitrogen atom (N-2) of pyrazole. This pathway for the formation of **8** is supported by the fact that conversion $8 \rightarrow 7$ is catalysed by hydrogen chloride generated from 2. Most probably, the conversion $8 \rightarrow 7$ occurs via 3, since 5 and 6 were formed when 2-propanol was added. The formation of 3 from 8 by elimination of the aglycon is ruled out owing to the lack of any conversion $8 \rightarrow 7$ in the presence of base. The parallel formation of 8 by way of the Lemieux-Nagabhushan reaction⁴, similar to that leading to isopropyl 3,4-di-O-acetyl-2-deoxy-2-hydroxyimino- α -D-erythropentopyranosides¹¹, cannot be ruled out. It is assumed that **8** is formed in the ${}^{1}C_{4}$ conformation, but the strong interactions of the dipoles of the substituents C-1,2,3 result in a change to the ${}^{4}C_{1}$ conformation.

The β -D-erythro- ${}^{1}C_{4}$ and α -D-erythro- ${}^{4}C_{1}$ structures, respectively, of 7 and 8 in solution were established as follows. The chemical shifts (7.16 and 7.00 p.p.m., respectively) of the resonances for H-1 of 7 and 8 indicate equatorial protons; the small difference in chemical shifts is due to different conformations of the sugar ring. For the same conformation but different spatial orientation of the aglycon, a difference of ~0.55 p.p.m. would be expected¹². The ${}^{3}J_{H,H}$ values indicate that H-4 is equatorial in 7 ($J_{4,5e}$ 1.5, $J_{4,5a}$ 3 Hz) and axial in 8 ($J_{4,5e}$ 3, $J_{4,5a}$ 9.5 Hz). It is remarkable that, despite its axial orientation, H-3 in 7 is more deshielded (0.4 p.p.m.) than the equatorial H-3 in 8. This is due to the effects of the axial substituents at C-1 and C-4.

The $[\alpha]_D$ values of 7 (-160°) and 8 (+230°) confirm the β and α configurations, respectively.

The 2-deoxy-2-hydroxyimino moiety is revealed by the nature of the ¹Hn.m.r. signals for H-1(s) and H-3(d), and by the i.r. absorptions for OH (3200 cm⁻¹) and C=N (1650 cm⁻¹) groups.

Bearing in mind the data about the influence of the orientation of the oxime hydroxyl group on the chemical shifts in the ¹H-n.m.r. spectra^{4,6,7}, as well as the fact that the $\Delta\delta$ H-1 value is small (0.16 p.p.m.), it is concluded that the configuration of the oxime group in 7 and 8 is Z.

The foregoing conclusions on the structures of 7 and 8 in solution were supported by the crystallographic data.

The numbering scheme, overall conformation, and molecular packing diagrams of molecules in the crystals of 7 and 8 are shown in Figs. 1 and 2. Tables I–V list the crystal data, bond lengths and angles, selected torsion angles, and hydrogen-bond distances and angles. The atomic parameters and anisotropic temperature factors have been deposited^{*}. The crystals of 7 are built from two symmetry-independent molecules A and B.

In each anomer, the pyranoid ring has the chair conformation. The puckering parameters^{13,14} for **8**, Q = 0.522(5) Å, $\theta = 24.7(5)$, and $\varphi = 300(1)^\circ$, indicate distortion of the 4C_1 conformation towards $B_{2,5}$ geometry. For molecules A and B of **7**, the respective parameters Q = 0.528(4) Å, $\theta = 170.2(4)$, $\varphi = 78(3)^\circ$, and Q = 0.473(4) Å, $\theta = 158.3(5)$, and $\varphi = 108(1)^\circ$ indicate deformation of the 1C_4 conformation in the direction between $B_{1,4}$ and 5S_1 and ${}^{2,5}B$, respectively. The distortion of the pyranoid rings of **8** and molecule B of **7** is significant. The main reasons for such deformations are the sp² hybridisation of C-2, syn-axial substituents on C-1 and C-3 in **8**, and syn-equatorial substituents on C-2 and C-3 in **7**.

The length of the C-5-O-5 bond in each anomer is slightly greater than that of the C-1-O-5 bonds in other pyranoses and pyranosides¹⁵, and the C-2-C-3 bonds are the shortest of all the C-C bonds in these pyranose rings. Most of the endocyclic

^{*}These data have been deposited with, and may be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/385/Carbohydr. Res., 172 (1988) 171-182.







Fig. 1. ORTEP drawings showing atom numbering for 1-(3,4-di-O-acetyl-2-deoxy-2-hydroxyimino- α -berythro-pentopyranosyl)pyrazole (a), and in molecule A (b) and B (c) of 1-(3,4-di-O-acetyl-2-deoxy-2hydroxyimino- β -D-erythro-pentopyranosyl)pyrazole hemihydrate. The non-hydrogen atoms are represented by 50% probability ellipsoids and the hydrogen atoms are drawn as spheres of arbitrary size.



Fig. 2. Molecular packing in the crystal of 1-(3,4-di-O-acetyl-2-deoxy-2-hydroxyimino- β -D-erythropentopyranosyl)pyrazole hemihydrate. The hydrogen atoms have been removed for clarity except those involved in hydrogen bonds (dashed lines).

TABLE I

CRYSTAL DATA^d

Compound	α anomer (8)	B anomer (7)
Formula	C ₁₂ H ₁₅ N ₃ O ₆	C12H15N2O205H2O
Lattice parameters:	12 15 5 6	12 15 5 6 2
a	6.811(2)	21.296(7) Å
Ь	11.456(4)	14.654(6) Å
с	9.244(3)	9.625(4) Å
β	105.86(2)°	
Unit-cell volume, V	693.8	3003.7 Å ³
Space group	P2,	P2,2,2,
Formula units per cell, Z	2	8
Calculated density, D	1.42	$1.35 g/cm^3$
Crystal dimensions	$0.10 \times 0.40 \times 0.65$	$0.40 \times 0.40 \times 0.55 \mathrm{mm}$
Number of independent reflections		
measured $(4.0 \le 2\theta \le 55.0^\circ)$	1675	3906
Number of reflections used in		
the refinement $[I > 1.96 \sigma(I)]$	1436	3049
Linear absorption coefficient, $\mu(MoK_{-})$	1.2	$1.2 \mathrm{cm}^{-1}$
Agreement factors ^b , R and R_w	0.056, 0.051	0.048, 0.043

^aEstimated standard deviations in parentheses. ^bR = $\Sigma ||F_0| - |F_c||/\Sigma ||F_0|$, $R_w = [\Sigma w(|F_0| - |F_c|)^2 / \Sigma w(F_0)^2]^{1/2}$, the function minimised was $\Sigma w(|F_0| - |F_c|)^2$ with $w = 1/\sigma_{F_0}^2$ and $\sigma_{F_0}^2 = \sigma_{counter}^2 + (0.002F_0)^2$.

TABLE	Ħ
INDLL	

	a Anomer (8)	β Anomer (7) Molecule			
		Α	В		
O-1N-2	1.358(5)	1.394(5)	1.386(4)		
O-2C-6	1.183(8)	1.190(5)	1.195(6)		
O-3-C-3	1.459(6)	1.438(4)	1.439(4)		
O-3C-6	1.352(6)	1.363(4)	1.354(5)		
O-4-C-4	1.430(5)	1.436(5)	1.453(4)		
O-4-C-8	1.339(7)	1.354(5)	1.359(5)		
0-5-C-1	1.397(5)	1.409(4)	1.392(4)		
O-5-C-5	1.431(5)	1.432(5)	1.431(5)		
O-6-C-8	1.188(7)	1.202(5)	1.194(5)		
N-1N-3	1.352(5)	1.351(5)	1.346(5)		
N-1C-1	1.473(6)	1.443(5)	1.456(5)		
N-1-C-12	1.330(6)	1.331(7)	1.333(6)		
N-2C-2	1.305(6)	1.278(5)	1.259(4)		
N-3-C-10	1.313(7)	1.321(7)	1.341(6)		
C-1-C-2	1.521(6)	1.521(5)	1.526(5)		
C-2C-3	1.476(6)	1.503(5)	1.493(5)		
C-3C-4	1.508(7)	1.531(5)	1.528(5)		
C-4-C-5	1.526(6)	1.509(6)	1.499(5)		
C-6C-7	1.503(9)	1.470(6)	1.458(7)		
C-8C-9	1.478(7)	1.459(8)	1.488(6)		
C-10-C-11	1.393(7)	1.357(9)	1,367(8)		
C-11-C-12	1.355(7)	1.366(8)	1.378(7)		

BOND LENGTHS (Å)^a

"Estimated standard deviations in parentheses.

C-C-C and C-C-O angles are not tetrahedral. Bond angles at O-5 are in the range 114.7(3)-116.0(3)°. The values for the exocyclic O-5-C-1-N-1 angles are slightly larger than that of C-2-C-1-N-1. As expected, the presence of the hydroxyimine groups results in an approximately planar configuration about C-2. In each structure investigated, the larger exocyclic C_{sp} - C_{sp} - N_{sp}^2 (C-1-C-2-N-2) valency angle is on the opposite side to the shorter C_{sp} - C_{sp}^3 - C_{sp}^3 (C-2-C-3) bond, although in 7 the vicinal groups at C-2 and C-3 are *syn*-equatorial. A similar situation exists in methyl 3,4-O-isopropylidene- β -L-*erythro*-pentopyranosid-2-ulose¹⁶.

All the planar acetoxy and pyrazole groups show a tendency for perpendicular orientation to the pyranoid rings. The hydroxyimine groups have the normal geometry with the C-1–C-2–O-1 torsion angles in the range -0.5(4)– +2.7(6) syn-form and with H–O-1 and C-2 trans. Bond lengths and valency angles in all five-membered pyrazole rings have expected values.

In the crystals, the hydrogens of the hydroxyimine groups and water molecules are involved in hydrogen bonding. In 8, there is only one linear, intermolecular hydrogen bond, whereas in 7, there is a net-work of linear and bifurcated

TABLE III

VALENCY ANGLES (DEGREES)⁴

	a Anomer (8)	β Anomer (7) Molecule			
		A	В		
N-2O-1H	105()	108(5)	109(5)		
C-3O-3C-6	116.7(4)	115.8(3)	117.1(3)		
C-4-O-4-C-8	117.1(4)	118.2(3)	116.7(3)		
C-1-O-5-C-5	114.8(3)	114.7(3)	116.0(3)		
N-3-N-1-C-1	119.4(4)	122.7(3)	119.9(3)		
N-3-N-1-C-12	111.2(4)	111.5(4)	113.0(3)		
C-1-N-1-C-12	128.2(4)	125.8(4)	127.1(3)		
O-1N-2C-2	112.9(4)	112.3(3)	112.7(3)		
N-1-N-3-C-10	105.0(4)	104.1(4)	103.5(4)		
O-5C-1N-1	110.9(3)	113.0(3)	112.8(3)		
0-5-C-1-C-2	112.8(4)	111.8(3)	113.9(3)		
N-1-C-1-C-2	109.5(4)	111.0(3)	108.4(3)		
N-2-C-2-C-1	125.3(4)	123.8(3)	122.6(3)		
N-2-C-2-C-3	115.2(4)	120.5(3)	119.2(3)		
C-1C-2C-3	119.5(4)	115.7(3)	118.0(3)		
0-3-C-3-C-2	106.7(4)	111.8(3)	108.1(3)		
0-3-C-3-C-4	108.5(4)	108.1(3)	110.7(3)		
C-2C-3C-4	110.6(4)	109.0(3)	112.8(3)		
0-4-C-4-C-3	110.6(4)	109.2(3)	107.8(3)		
0-4-C-4-C-5	105.4(4)	108.7(3)	108.3(3)		
C-3C-4C-5	110.4(4)	108.8(3)	109.9(3)		
0-5-C-5-C-4	107.4(3)	112.2(3)	111.7(3)		
0-2C-6O-3	123.5(5)	122.9(4)	121.9(4)		
0-2C-6C-7	126.7(6)	127.5(4)	127.0(4)		
O-3C-6C-7	109.7(5)	109.6(3)	111.2(4)		
0-4-C-8-0-6	122.3(5)	123.6(4)	123.3(4)		
0-4-C-8-C-9	113.2(4)	112.1(4)	110.7(4)		
O-6-C-8-C-9	124.6(5)	124.3(4)	125.9(4)		
N-3-C-10-C-11	111.4(5)	112.4(5)	112.1(5)		
C-10-C-11-C-12	104.5(5)	105.0(6)	105.2(5)		
N-1-C-12-C-11	107.9(4)	107.0(5)	106.2(4)		
H-1-O-W-H-2		10	05(5)		

"Estimated standard deviations in parentheses.

hydrogen bonds. The hydrogen atoms of the hydroxyimine groups form linear bonds only, and both hydrogen atoms of the water molecule participate in the system of bifurcated hydrogen bonds.

TABLE IV

SELECTED	TORSION	ANGLES	DEGREES	۱ª
OFFECT FO	10101011	111.00000		,

	α Anomer (8)	β Anomer (7) Molecule		
		A	B	
C-1-C-2-C-3-C-4	-34.2(6)	48.8(5)	33.7(4)	
C-2C-3C-4C-5	48.8(5)	53.6(6)	-45.4(4)	
C-3-C-4-C-5-O-5	-63.8(5)	59.3(6)	58.1(4)	
C-4-C-5-O-5-C-1	64.4(5)	-58.6(5)	-59.8(4)	
C-5-O-5-C-1-C-2	-48.0(5)	49.7(6)	44.8(4)	
O-5-C-1-C-2-C-3	32.8(6)	46.2(6)	-32.3(4)	
C-5-O-5-C-1-N-1	75.2(5)	76.4(5)	-79.3(4)	
O-5-C-1-N-1-N-3	43.6(5)	83.0(7)	89.1(4)	
O-5C-1C-2N-2	-147.2(6)	132.8(6)	151.5(5)	
N-1-C-1-C-2-N-2	88.9(6)	-100.0(6)	-82.1(4)	
C-1-C-2-N-2-O-1	-1.4(7)	2.7(6)	-0.5(4)	
C-2-N-2-O-1-H	-171(-)	-168(3)	170(5)	
C-1C-2C-3O-3	83.7(5)	168.3(5)	156.5(4)	
C-2-C-3-O-3-C-6	147.0(5)	112.8(5)	155.2(4)	
N-2-C-2-C-3-O-3	-96.3(5)	-10.8(5)	-27.2(4)	
C-5-C-4-C-3-O-3	-68.0(5)	-175.3(6)	-166.7(4)	
C-2-C-3-C-4-O-4	165.1(5)	65.0(6)	72.4(4)	
O-3-C-3-C-4-O-4	48.3(5)	-56.8(6)	-48.8(4)	
O-5-C-5-C-4-O-4	176.8(5)	-59.5(6)	-59.5(4)	

"Estimated standard deviation in parentheses.

TABLE V

hydrogen-bond lengths (Å) and angles (degrees)^a

$D-H\cdots A$ (symmetry code)	D····A	D-H	$H \cdots A$	<i>≰ DHA</i>	$\neq A_1 - H - A_2$
α Anomer (8)					
$O-1-H\cdots N-3(1 + x, y, z)$	2.780(5)	0.99(-)	1.81(-)	165(-)	
β Anomer (7)					
$O-1B-H\cdots N-2A(x, y, z)$	2.800(4)	0.86(7)	1.94(7)	178(7)	
$O-1A-H\cdots O-W(\frac{1}{2}-x, 1-y, -\frac{1}{2}+z)$	2.718(5)	1.01(8)	1.71(8)	173(7)	
.N-2B (x, y, z)	2.877(5)		1.98(4)	151(4)	
O-W-H-1		0.97(4)			70(1)
(0.3B(x, y, z))	3.306(4)		2.52(4)	138(3)	
$O-2B(\frac{1}{2} - x, 1 - y, \frac{1}{2} + z)$	3.097(5)		2.60(5)	131(5)	
О-W-H-2		0.69(5)			81(1)
O-6B $(\frac{1}{2} - x, 1 - y, \frac{1}{2} + z)$	3.087(5)		2.49(5)	148(5)	

^aValues in parentheses are estimated standard deviations. A and B in this numbering scheme indicate atoms from the molecule A or B, respectively.



molecule B

All parameters of these bifurcated hydrogen bonds agree well with those presented by Jeffrey and co-workers¹⁷⁻¹⁹.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined (Hilger-Watt instrument) for solutions in chloroform (c 0.5). T.I.c. was performed on Silica Gel G with A, carbon tetrachloride-acetone (3:1). Column chromatography was performed on Kieselgel (<0.08). ¹H-N.m.r. spectra (CDCl₃, internal Me₄Si) were recorded with a Tesla-BS 487C (80 MHz) spectrometer. I.r. spectra were recorded for Nujol mulls with a Perkin–Elmer 257 spectrophotometer.

X-Ray structure determination. — The space groups were determined from oscillation and Weissenberg photographs. All measurements were made on a Syntex $P2_1$ diffractometer equipped with a scintillation counter and a graphite monochromator using MoK radiation ($\lambda = 0.71069$ Å). The cell parameters were determined from a least-squares refinement of the setting angles of 15 reflections. Intensities of independent reflections were measured with the variable θ -2 θ scan technique. The scan rate varied from 2.0 to 29.3°/min, depending on the intensity. The intensities were not corrected for absorption.

Both structures were solved by direct methods. The E-maps showed the positions of all heavy atoms, which were refined by the block diagonal least-squares routine with isotropic and, subsequently, anisotropic temperature factors. The methyl, hydroxyl, and water (for 7) hydrogens were found from ΔF syntheses, and the positions of the remaining hydrogens were calculated based on the geometry of the molecules (C-H and N-H = 0.95 Å). Full-matrix least-squares refinement of heavy-atom parameters for 8 and including hydroxyl and water hydrogens with

isotropic temperature factors for 7 was then performed. Neutral atom scattering factors were those listed in International Tables for X-Ray Crystallography²⁰. The anomalous dispersion was included for the oxygens. Calculations were performed using the following programs: MULTAN-80²¹, Syntex XTL/XTLE²², PUCK 2²³, and ORTEF²⁴. The crystallographic data are summarised in Table I.

Dimeric 3,4-di-*O*-acetyl-2-deoxy-2-nitroso- β -D-arabinopyranosyl chloride (2) had m.p. 112–114°, $[\alpha]_D^{20} -206°$ (c 0.5, chloroform); lit.¹¹ m.p. 126–128°, $[\alpha]_D -211.6°$; lit.²⁵ m.p. 116–121°, $[\alpha]_D -203.2°$.

Isopropyl 3,4-di-O-acetyl-2-deoxy-2-hydroxyimino- β -D-*erythro*-pentopyranoside (5) and its α anomer (6) were prepared according to the literature procedure¹¹: β anomer, syrup, $[\alpha]_{D}^{20} - 140^{\circ}$, $R_{\rm F} 0.48$ (solvent A) (lit.¹¹ $[\alpha]_{\rm D} - 135^{\circ}$); α anomer, syrup, $[\alpha]_{D}^{20} + 179^{\circ}$, $R_{\rm F} 0.56$ (lit.¹¹ $[\alpha]_{\rm D} + 182.8^{\circ}$). The ¹H-n.m.r. spectra of 5 and 6 were identical with those reported¹¹.

3,4-Di-O-acetyl-D-arabinal (1). — To a solution of sodium acetate (35 g) and acetic acid (115 mL) in water (200 mL) was added a solution of zinc dust (70 g) and copper(II) sulphate pentahydrate (7 g) in water (23 mL) at -5° . To this suspension, 2,3,4-tri-O-acetyl- β -D-arabinopyranosyl bromide^{26,27} (34 g) was added gradually, and the mixture was stirred vigorously, initially for 3 h at -5° then for 24 h at +20°. The mixture was filtered, diluted with water (400 mL), and extracted with chloroform (4 × 100 mL), and the combined extracts were washed successively with water (100 mL), aqueous saturated sodium carbonate (2 × 50 mL), and water (100 mL), and then concentrated. T.I.c. (solvent A) showed the syrupy crude product (28 g) to contain three species ($R_F 0.80$, 0.62, and 0.35). Fractional distillation gave 3,4-di-O-acetyl-D-arabinal (1; 13 g, 65%), b.p. 80–85°/8 mmHg, $[\alpha]_D^{20}$ +260° (c 0.5, chloroform), $R_F 0.80$ (solvent A); lit.⁸ $[\alpha]_D^{20}$ +265°.

1-(3,4-Di-O-acetyl-2-deoxy-2-hydroxyimino-β- (7) and -α-D-erythro-pentopyranosyl)pyrazole (8). — (a) A solution of 2 (3 g, 11 mmol) and pyrazole (22 mmol, 1.5 g) in acetonitrile (30 mL) was kept for 48 h at ~20°. T.l.c. (solvent A) then revealed the complete conversion of 2 into two products (R_F 0.49 and 0.39). The solution was concentrated, and a solution of the syrupy residue in chloroform (150 mL) was washed with water (3 × 40 mL), dried (MgSO₄), and concentrated. The residue was crystallised from carbon tetrachloride-acetone (3:1) to give, first, 8 (31%), m.p. 162–163°, $[\alpha]_D^{20}$ +230°, R_F 0.37; ν_{max} 3250 (OH), 1650 (CN), and 1745 cm⁻¹ (ester CO); δ for H-1,3,4,5e,5a were 7.00 (s), 6.50 (d), 5.19 (m), 3.70 (dd), and 3.80 (dd), respectively; $J_{3,4} \sim 4$, $J_{4,5e} \sim 3$, $J_{4,5a} \sim 9$, and $J_{5e,5a} \sim 11$ Hz.

Anal. Calc. for C₁₂H₁₅N₃O₆: C, 48.48; H, 5.08; N, 14.14. Found: C, 48.38; H, 5.01; N, 14.10.

The second fraction was 7 (34%), m.p. 120–123°, $[\alpha]_D^{20} - 160^\circ$, $R_F 0.42$; ν_{max} 3220 (OH), 1660 (CN), and 1745 cm⁻¹ (ester CO); δ for H-1,3,4,5*e*,5*a* were 7.16 (s), 3.55 (d), 5.43 (m), 4.10 (dd), and 3.83 (dd), respectively; $J_{3,4} \sim 4$, $J_{4,5e} \sim 1.5$, $J_{4,5a} \sim 3$, and $J_{5e,5a} \sim 14$ Hz.

Anal. Calc. for C, 48.45; H, 5.04; N, 14.10.

(b) A solution of 2 (5.5 mmol, 1.5 g) and pyrazole (11 mmol, 0.75 g) in

acetonitrile (15 mL) was boiled under reflux (~30 min) until 2 was transformed into one product, R_F 0.49 (solvent A), and then concentrated. The residue was then processed as in (a) to give only 7 (65%).

(c) A solution of 8 (0.25 mmol) and hydrogen chloride or 2, as catalyst, in acetonitrile (7 mL) was boiled under reflux for 1 h. T.l.c. then indicated complete conversion of 8 into 7, whereas 5-7 remained unchanged under these conditions.

(d) A solution of 8 (3 mmol) and 2-propanol (1 mL) in acetonitrile (15 mL) was boiled under reflux for 1.5 h. Three products (R_F 0.42, 0.48, and 0.56) were then present. The mixture was processed as in (a) and column chromatography (solvent A) gave 7, 5, and 6.

(e) A solution of 7 or 8 (0.25 mmol) in acetonitrile (5 mL) or in acetonitrile with a catalytic amount of pyrazole or triethylamine was boiled under reflux for 2 h. T.l.c. then indicated that no reaction had occurred.

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