SYNTHESIS OF (4'R)- AND (4'S)-5-(2',2'-DIMETHYL-1',3'-DIOXOLAN-4'-YL)-3-PHENYL-4,5-DIHYDRO-1,2,4-OXADIAZOLES AND (4'R)-5-(2',2'-DIMETHYL-1',3'-DIOXOLAN-4'-YL)-3-PHENYL-1,2,4-OXADIAZOLE

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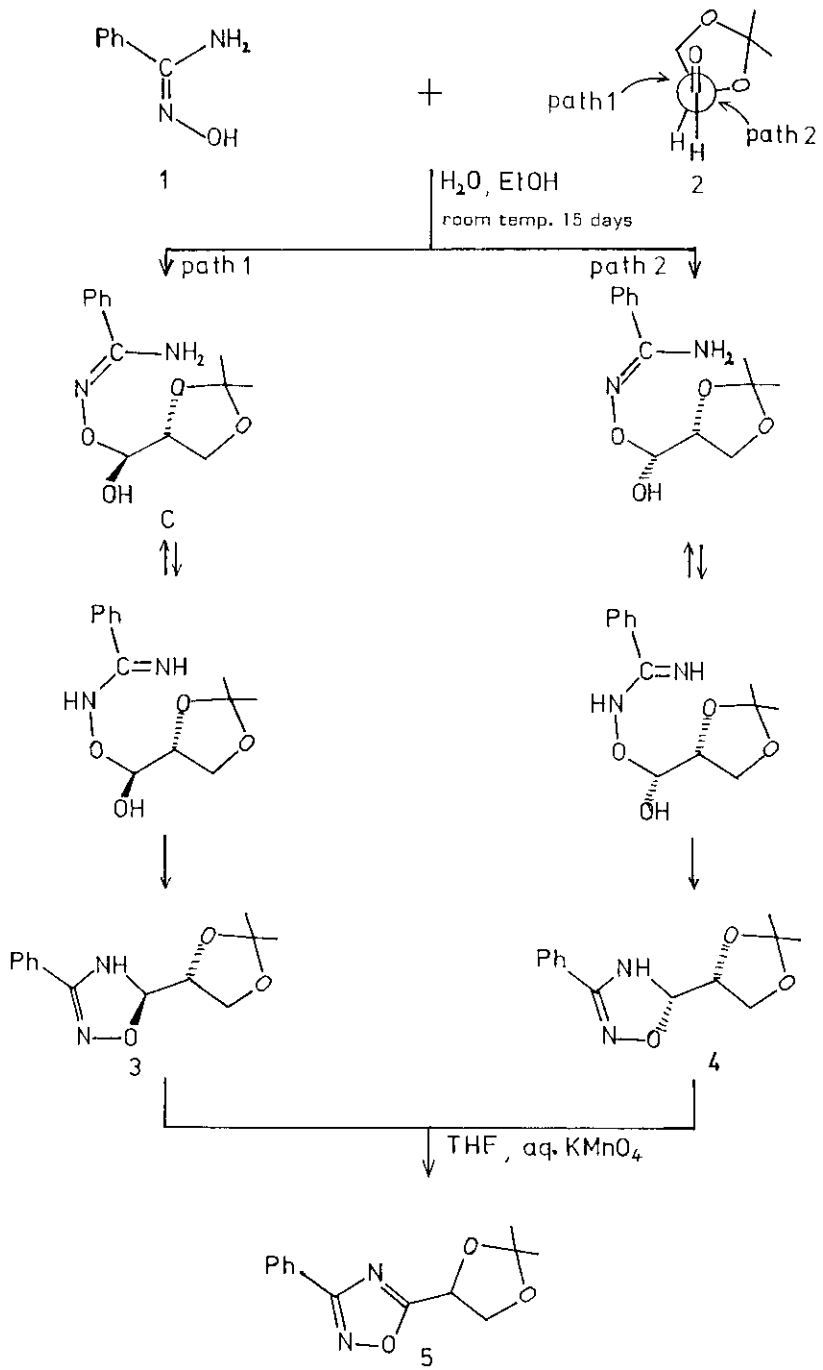
Abstract - Chiral 3,5 disubstituted 4,5-dihydro-1,2,4-oxadiazoles (**3**, **4**) have been prepared starting from benzamidoxime (**1**) and (R)-(-)-2,3-O-isopropylideneglyceraldehyde (**2**). The structure of **3** was established as (4'R)-5-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazole by X-ray diffraction analysis on a single crystal. Mild potassium permanganate oxidation of a mixture of **3** and **4** gave the corresponding 1,2,4-oxadiazole (**5**).

INTRODUCTION

In 1985, Hennen and Robins [1] synthesized 5-(β-D-ribofuranosyl)-1,2,4-oxadiazole-3-carboxamide and tested its activity. This compound was shown to give inhibition of leukemid L 1210 and P 388 in cell culture. It also showed a virus rating of 0.38 and 0.51 against vaccinia and HSV-2 viral lines respectively with very little cellular toxicity. Recently, Tronchet et al. [2] reported the preparation of 1,2,5,6-di-O-isopropylidene-3-(5-methyl-1,2,4-oxadiazol-3-yl)-α-D-gluco- and α-D-allofuranose starting from the sugar amidoximes. This stereoisomeric mixture of 4,5-dihydro-1,2,4-oxadiazoles was aromatized to yield 1,2,4-oxadiazoles. No other compounds of this kind are known in the literature. It, therefore, appeared attractive to synthesize 1,2,4-oxadiazoles having a carbohydrate moiety attached at position 5 with a view to study the chemistry and the biological activity of 4,5-dihydro-1,2,4-oxadiazoles (**3**, **4**). X-ray crystal structure determination of **3** established the configuration and conformation. An easy transformation of a mixture of **3** and **4** to **5** is also described (Scheme 1).

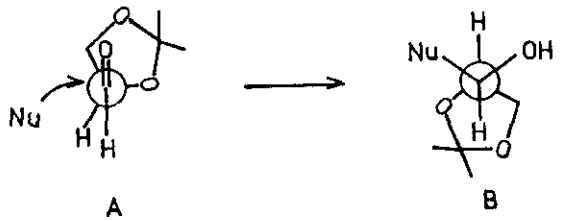
RESULTS AND DISCUSSION

Reaction of benzamidoxime (**1**)[3] with (R)-2,3-O-isopropylideneglyceraldehyde (**2**)[4], using either water or water-ethyl alcohol mixture as a solvent gave two diastereoisomeric Δ^2-1,2,4-oxadiazolines in an approximate ratio of 2:1. Separation of both of products was achieved by flash chromatography.


Ph
NH2
C
N
OH
1
path1
path2
H
H
2
H2O, EtOH
room temp. 15 days
path 1
path 2
O
OH
C
NH
HN
3
4
THF, aq. KMnO4
N
5

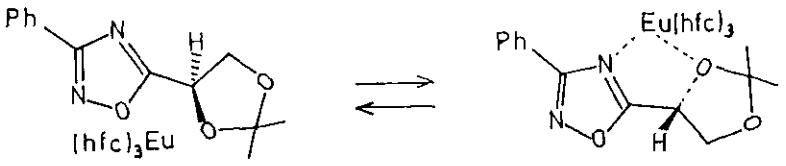
The ^{1}H nmr spectrum of the compound (3) showed signals at δ 5.44 and 5.08 attributed to H-5 and NH of oxadiazoline. Deuterium oxide exchange caused the loss of 4.5 Hz coupling giving a doublet (J = 5.5 Hz) for H-5. This coupling constant between H-5 and H-4' suggests that the dihedral angle between H-5-C-5 and H-4'-C-4' may either be about 35° or 125°. The X-ray data of 3 provided a dihedral angle of 114°. Addition of the shift reagent, tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III) [Eu(hfc)$_3$] caused H-5 at δ 5.44 to 5.58 giving a sharp doublet of doublet (J = 6.0Hz and 2.0Hz). Further addition of the shift reagent caused more downfield shift of this signal without showing any presence of another enantiomer. *It is, therefore, apparent that the compound 3 is a single compound.* This view was confirmed by X-ray analysis of 3 and proved the structure as (4'R, 5R)-5-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazole. The close proximity of the torsion angle between H-5-C-5 and H-4'-C-4' obtained in solution and solid phase indicates the stability of the conformation described on the scheme 1.

The predominant formation of diastereoisomer 3 compared to 4 might be explained. For carbonyl compounds with an alkoxyl group in position α with respect to the formyl group, Felkin [5] and Anh [6] have suggested that the large substituent is assumed to be arranged perpendicularly to the carbonyl group. Consequently, the nucleophilic reagent may predominantly attack the carbonyl group from the least hindered face giving a major product with anti configuration. It has been established earlier [7,8,9] that nucleophilic addition to formyl group of (R)-2,3-O-isopropylideneglyceraldehyde occurs preferentially as shown in scheme 2 and gives a mixture with the predominance of the antistereoisomer B. Similarly, in our case, the oxygen atom of benzamidoxime could approach the formyl group of compound 2 from the side as shown in path I (scheme 1). This will give an intermediate C which cyclizes into 3 following the mechanism described by Srivastava et al. [10].



Scheme 2

The other not crystalline product 4, as expected, was formed in limited quantity through path II (Scheme 1). Its structure has been determined by mass spectrum (m/z = 248) and ^{1}H nmr. Deuterium oxide exchange gave a doublet for H-5 (J = 3.0 Hz) indicating a dihedral angle of about 50° or 115° between H-5-C-5 and H-4-C-4 of 4. The mixture of oxadiazolines 3 and 4 were easily oxidized to 5. The ^{1}H nmr spectrum of this product 5 showed a triplet (δ: 5.38, J = 6.0 Hz) which is shifted downfield by addition of Eu (hfc)$_3$. This triplet showed slight splitting which may due to coupling of the adjacent protons or to the possibility of an equilibrium between the two conformations F and G as shown below. Such a ligand exchange has been reported by Forsberg [11]. Since there was only one set of signal for H-4', the compound 5 is a single enantiomer.



F G

MOLECULAR STRUCTURE

X-ray crystal structure determination of **3** was carried out to determine the configuration at C-4' and C-5 (Scheme 1 numbering). A crystal of 0.5 x 0.6 x 0.6 mm was used to collect intensities data using $CuK\bar{\alpha}$ radiation (graphite monochromator). Crystal data are in Table 1. Of the 1465 independent reflections examined, only 1411 were considered as observed according to the two fulfilled conditions: $I > 1.4\,\sigma(I)$ and $I > 1.3\,I$ background. Lorentz and polarization corrections were applied, but no absorption correction was made. The structure was solved by direct method [12] and refined anisotropically by full matrix procedure. The function minimized was $\Sigma\ W(|Fo|-|Fc|)^2$ where $W = (a + b\,|Fo|)^{-2}$ calculated from $|\overline{\Delta F}|$ Vs $|\overline{Fo}|$ curves. Hydrogen atoms were located on a difference Fourier map. The final refinement involved the x, y, z, β_{ij} parameters for the non-H atoms and x, y, z for the H atoms with isotropic B equal to the B eq of bearing C or N atoms. The final R value was 0.048 for the 1411 observed reflections where $R = \Sigma\ ||Fo|-|Fc|| / |Fo|$, and a weighted $R_w = [\Sigma\ W(|Fo|-|Fc|)^2 / W\,|Fo|^2)^{1/2}$ was 0.071.

Atomic coordinated are in Table 2. The drawing of the molecule with atom labeling (Figure 1), was obtained by means of ORTEP [13]. Main bond lengths and angles are in table 3. The hydrogen atom H(11) of the oxadiazoline ring is facing upward on the drawing and the dihedral angle H(11)-C(6)-C(2)-H(2) is 114°. The dihedral angle between the mean square planes of the phenyl ring and the central ring is 21.7°. Also, there is a torsion angle of 70.9° between both heterocycles (Figure 2).

As expected, C(8)-C(7) has a bond length of 1.466 Å which is intermediate between a C-C single and C=C double bond. The bond length of 1.371 Å has been found for C(7)-N(2) giving a clear indication of a partial double bond character in it. The intermolecular interaction (Table 3) also suggests that there is no hydrogen bonding between $\rightleftharpoons$NH of one molecule and = N- of an other molecule in the crystal.

Table 1. Crystallographic data for compound **3**

Molecular Formula	$C_{13}H_{16}N_2O_3$
Molecular Weight	248.3
Solvent of Crystallization	Benzene
Crystal System	Orthorhombic
Space Group	$P\,2_1\,2_1\,2_1$
a/ Å	5.2170 (5)
b	14.029 (1)
c	17.257 (2)
Z	4
Dc (g/cm^{-3})	1.306
V (Å^3)	1263.0 (4)

Table 2. Relative atomic coordinates and thermal B_{eq} parameters of non-hydrogen atoms. $B_{eq} = 4/3\Sigma i\Sigma j\ \beta_{ij}\ a_i\ a_j$

Atom.	x	y	z	B_{eq}(Å^2)
O (1)	0.5024 (5)	0.8420 (1)	0.3691 (1)	5.5
O (2)	0.2118 (4)	0.7777 (1)	0.2870 (1)	4.6
O (3)	0.5308 (4)	0.6229 (2)	0.3494 (1)	5.2
N (1)	0.6145 (5)	0.5498 (2)	0.4029 (1)	4.4
N (2)	0.1974 (5)	0.5757 (2)	0.4235 (2)	4.6
C (1)	0.3836 (6)	0.8560 (2)	0.2959 (2)	4.5
C (2)	0.1701 (6)	0.7330 (2)	0.3597 (2)	4.1
C (3)	0.3209 (9)	0.7929 (2)	0.4169 (2)	5.9
C (4)	0.5833 (9)	0.8485 (5)	0.2350 (3)	8.5
C (5)	0.2363 (9)	0.9475 (2)	0.2923 (3)	7.3
C (6)	0.2556 (5)	0.6301 (2)	0.3537 (2)	4.2
C (7)	0.4132 (5)	0.5243 (2)	0.4409 (1)	3.7
C (8)	0.4205 (5)	0.4507 (2)	0.5011 (1)	3.7
C (9)	0.6160 (5)	0.3825 (2)	0.4995 (2)	4.4
C (10)	0.6264 (6)	0.3127 (2)	0.5566 (2)	5.0
C (11)	0.4468 (7)	0.3112 (2)	0.6146 (2)	5.0
C (12)	0.2521 (7)	0.3771 (2)	0.6162 (2)	4.9
C (13)	0.2394 (6)	0.4481 (2)	0.5593 (2)	4.4

Table 3. Main bond lengths (Å) and angle (°)

N (1) - O (3)	1.448 (3)	C (6) - O (3)	1.441 (3)
C (7) - N (1)	1.289 (3)	C (6) - N (2)	1.457 (3)
C (7) - N (2)	1.371 (3)	C (2) - O (2)	1.419 (3)
C (8) - C (7)	1.466 (3)	C (2) - C (6)	1.515 (4)
C (9) - C (8)	1.398 (4)	C (3) - O (1)	1.433 (5)
C (10) - C (9)	1.390 (4)	C (3) - C (2)	1.516 (5)
C (11) - C (10)	1.371 (4)	C (1) - O (2)	1.427 (3)
C (12) - C (11)	1.373 (4)	C (1) - O (1)	1.420 (3)
C (13) - C (8)	1.379 (4)	C (4) - C (1)	1.485 (5)
C (13) - C (12)	1.401 (4)	C (5) - C (1)	1.497 (5)

N (1) - O (3) - C (6)	108.5 (2)	C (8) - C (13) - C (12)	119.7 (3)
C (2) - O (2) - C (1)	109.9 (2)	O (3) - C (6) - N (2)	102.4 (2)
C (3) - O (1) - C (1)	106.9 (3)	O (3) - C (6) - C (2)	111.3 (2)
O (3) - N (1) - C (7)	108.0 (2)	N (2) - C (6) - C (2)	112.4 (2)
C (7) - N (2) - C (6)	106.6 (2)	O (2) - C (2) - C (6)	108.4 (2)
N (1) - C (7) - N (2)	114.3 (2)	O (2) - C (2) - C (3)	104.6 (2)
N (1) - C (7) - C (8)	122.4 (2)	C (6) - C (2) - C (3)	114.8 (3)
N (2) - C (7) - C (8)	123.2 (2)	O (1) - C (3) - C (2)	103.6 (2)
C (7) - C (8) - C (9)	119.1 (2)	O (2) - C (1) - O (1)	105.3 (2)
C (7) - C (8) - C (13)	121.1 (2)	O (2) - C (1) - C (4)	108.0 (3)
C (9) - C (8) - C (13)	119.8 (2)	O (2) - C (1) - C (5)	109.5 (3)
C (8) - C (9) - C (10)	119.7 (3)	O (1) - C (1) - C (4)	108.3 (3)

C (9) - C (10) - C (11)	120.1 (3)	O (1) - C (1) - C (5)	112.3 (3)
C (10) - C (11) - C (12)	120.7 (3)	C (4) - C (1) - C (5)	113.1 (4)
C (11) - C (12) - C (13)	119.9 (3)		

Hydrogen intermolecular interaction:

N (2) - H (1)..... N (1^i) i = x - 1, y, z

^{d}N (2)..... N (1^i) = 3.083 (3) Å

N (2) - H (1)..... N (1^i) = 133 (4)°.

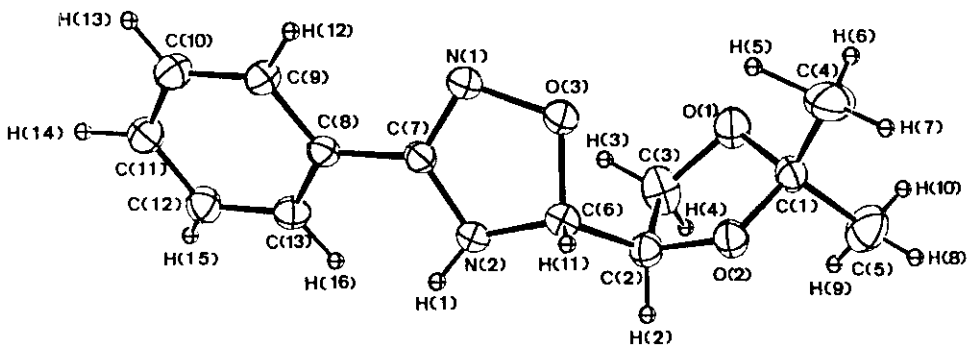


Figure 1. ORTEP drawing of the molecule 3 . Thermal ellipsoids are sealed at the 25 % probability level. The hydrogen atoms are sealed arbitrarity. The numbering system of 3 in this drawing is different that of Scheme I.

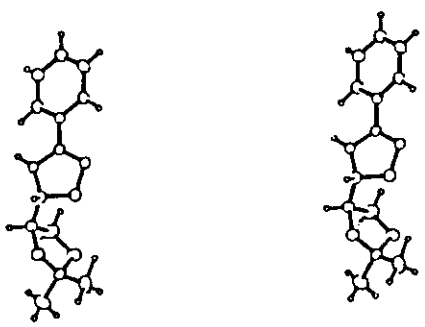


Figure 2. ORTEP stereoscopic view.

EXPERIMENTAL

Melting points were taken on a Büchi apparatus and are uncorrected. The evolution of the reactions was followed on thin layer chromatography. ^{1}H Nmr spectra were determined in $CDCl_3$ with TMS as an internal standard on a Varian EM 360 or a Brucker WP 80 CW spectrometer. Mass spectra were recorded on a Nermag R 10 105 spectrometer. Rotatory power was run on a Perkin-Elmer 241 polarimeter.

(4'R)- and (4'S)-5-(2',2'-Dimethyl-1',3'-dioxolan-4'-yl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazoles (3) and (4) 2,3-O-Isopropylidene-D-glyceraldehyde (0.6 g, 4.6 mmol) was added to a solution of benzamidoxime (1) (0.2g, 1.47 mmol) in water (15 ml). After flushing with N_2, the flask was stoppered and the contents were stirred at room temperature for 15 days. Thin layer chromatography, using ethyl acetate - hexane (1:1), was revealed two new spots of Rf values 0.60 and 0.45 besides the starting 1 (Rf = 0.16). The contents were extracted with chloroform (3 x 15 ml), dried over Na_2SO_4, filtered and solvent was evaporated to give 0.53 g of a viscous liquid. Chromatography over silica gel employing ethyl acetate - hexane (1:9) and gradually increasing the polarity separated 0.072 g, 0.036 g and 0.05 g of products having Rf values of 0.60, 0.45 and 0.16 respectively.

Compound 3: The fastest moving spot (26 %) was crystallized from benzene. The crystals shrank at 99~100°, melted at 102° but the melt became clear at 105°C: $[\alpha]^{22}$ - 14° ($CHCl_3$, c = 0.4); ir (KBr) ν_{max} 3260 cm^{-1}: ^{1}H nmr (60 MHz, $CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.78-4.45 (m, 3H, $-CH_2O$, CHO), 5.08 (b, 1H, -NH-), 5.44 (unresolved dd, 1H, -CH-, W/2 = 10 Hz) and 7.25-7.83 (m, 5H, Ar); ($CDCl_3$ + D_2O):δ 5.44 (d, 1H, -CH-, J = 5.5 Hz): ms: M^+ m/z 248 (1.6 %), 233 (3.49), 173 (5.78), 147 (46.33), 119 (50.94), 104 (15.61), 91 (11.98), 77 (100), 45 (72.44).

Compound 4: The second spot (13 %): viscous liquid: $[\alpha]^{18}$ - 28° ($CHCl_3$, c = 0.5); ^{1}H nmr (60 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.85 - 4.45 (m, 3H, $-CH_2O-$ and -CH-O-), 4.88 (b, 1H, -NH), 5.75 (t, 1H, -CH-, W/2 = 6 Hz), 7.33 - 7.83 (m, 5H, Ar): ms: M^+ m/z 248 (1.25 %), 233 (3.35), 173 (4.65), 147 (56.13), 119 (69.96), 104 (8.76), 91 (4.08), 77 (37.71), 45 (100).

(4'R)-5-(2',2'-Dimethyl-1',3'-dioxolan-4'-yl)-3-phenyl-1,2,4-oxadiazole (5)- The crude material, obtained from the compounds 1 (0.4 g, 2.9 mmoles) and 2 (2.9 g, 22.4 mmoles) was dissolved in tetrahydrofuran (15 ml); to this solution was added an aqueous saturated solution of potassium permanganate until the red color persisted. After filtration of the brown precipitate, the filtrate was extracted with ether (50 ml), dried over Na_2SO_4 and evaporated. The viscous residue was purified by chromatography over silica gel using ethyl acetatehexane (5:95) to give 0.216 g (30 %) of pure oxadiazole 5 which could be crystallized from ethanol-water: mp 43°C; $[\alpha]^{19}$ + 29° ($CHCl_3$, c = 0.7); ^{1}H nmr (80 MHz, $CDCl_3$): δ 1.51 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 4.35 4.53 (two dd, J = 5.7 and 3.0 Hz, 2H, CH_2), 5.38 (t, J = 6.0 Hz, 1H, -CH-), 7.38 - 7.65 (m, 3H,Ar), 7.98 8.25 (m, 2H, Ar). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73, N, 11.38. Found: C, 63.81; H, 5.89;N, 11.28.

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