The Reaction of Phenylglyoxal with 2-Aminoalcohols. Rearrangement of 2-Acyloxazolidines to 2-Hydroxy-5,6-dihydro-1,4-oxazines

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The reactions of phenylglyoxal hydrate with (*R*)-phenylglycinol and with (1*S*,2*R*)-norephedrine were investigated. The expected 2-benzoyloxazolidines **3** and **2a**, respectively are initially formed, and undergo a fast, spontaneous stereospecific rearrangement to the corresponding 2-hydroxy-3-phenyl-5,6-dihydro-1,4-oxazines **4** and **5** respectively. The mechanism of this new rearrangement is discussed. The structures and stereochemistry of **4** and **5** were established by X-ray diffraction analysis.

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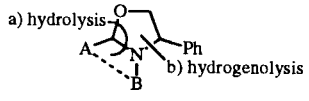
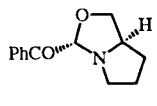
The successful double use of proline as a chiral auxiliary and removable tether in cycloadditions [1] motivated the search for other 5-membered heterocycles which would extend the scope of this synthetic methodology. 4-Phenyloxazolidines functionalized at position 2 seem an attractive possibility as disconnection of the reaction components would be easily achieved by cleavage of the ring itself (see Figure 1). This point is important as groups

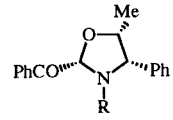
Figure 1



such as enamines or enol ethers become non-removable after participation in cycloadditions. Oxazolidines are readily made by the reaction of carbonyl compounds with 2-aminoalcohols. Although the reaction of ethanolamine with 1,2-dicarbonyl compound is quite complex [2] and affords a plethora of products which does not include the desired 2-acyloxazolidines, it was hoped that with phenlglyoxal, due to the great difference of reactivity between the two carbonyls, 2-acyloxazolidines would be formed. Indeed the reaction of phenylglyoxal with (*S*)-prolinol [3] yielded **1**, and with (1*R*,2*S*)-norephedrine it yielded compound **2a** which was transformed to **2b** [4,5]. Both **1** and **2b** have been used as chiral auxiliaries in Gringard reactions of their benzoyl groups [3-5], and so were, very recently, some aminal analogs [6,7].

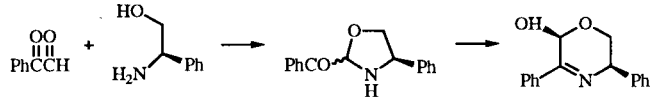


1



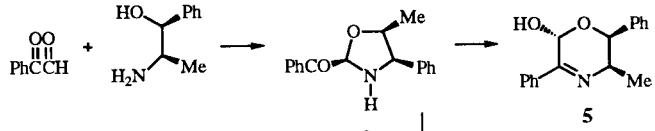
2a, R = H
b, R = *t*-Boc

2-Benzoyl-5-phenyloxazolidine (**3**), which is appropriate for our purpose, would thus be available from the reaction of phenylglyoxal with phenylglycinol. This reaction indeed gave (with (*R*)-phenylglycinol) 87% yield of a crystalline product of the expected composition $C_{16}H_{15}NO_2$, which was first assigned as **3**. However both the chemical characteristics (no reaction with $(t\text{-BOC})_2O$ and the spectral properties (no ketone absorption in the ir and ^{13}C nmr spectra) suggested a different structure. An X-ray analysis (Figure 2) established the structure as (2*S*,5*R*)-5,6-dihydro-3,5-diphenyl-2-hydroxy-1,4-oxazine (**4**).



3 **4**

This result is in disagreement with the report by Agami [3] on the reaction with norephedrine. We therefore reran it (using (1*S*,2*R*)-norephedrine) and found that **2a** is initially formed, and if *immediately* reacted with $(t\text{-BOC})_2O$ it gives **2b**. However, upon crystallization or standing in solution (THF) at room temperature for 90 minutes, the oily **2a** rearranged to a crystalline isomer. Its structure was determined (X-ray analysis, Figure 3) as (2*R*,5*R*,6*S*)-5,6-dihydro-3,6-diphenyl-2-hydroxy-5-methyl-1,4-oxazine (**5**).



2a **5**

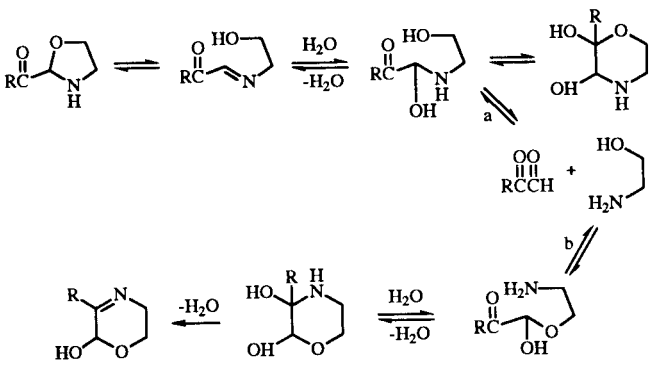
2b

Consequently we looked again at the reaction of phenylglyoxal with phenylglycinol, and with hplc analysis we have detected the initial formation of **3** and its rearrangement to **4**. The rearrangement in this case was much faster than the one of **2a** to **5**, hence it was not possible to trap **3** as the *t*-BOC derivative.

It therefore emerges that 2-acyloxazolidines rearrange spontaneously to 5,6-dihydro-1,4-oxazines. The rearrangement requires the cleavage of a carbon-nitrogen bond and formation of a new one. The product oxazine is probably the most stable component of a complex equilibrium system (partly depicted in Scheme 1), which also contains reversion to aminoalcohol and dicarbonyl com-

pound. The most rational pathway indeed starts with reaction of the amino group with the aldehydic carbonyl (path a) and leads to acyloxazolidines. The thermodynamic control however directs the reaction through path b and the

Scheme 1



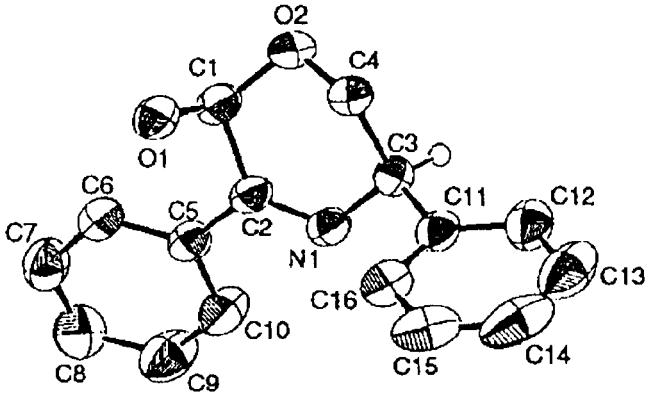


Figure 1. X-ray crysyal structure of **4**.

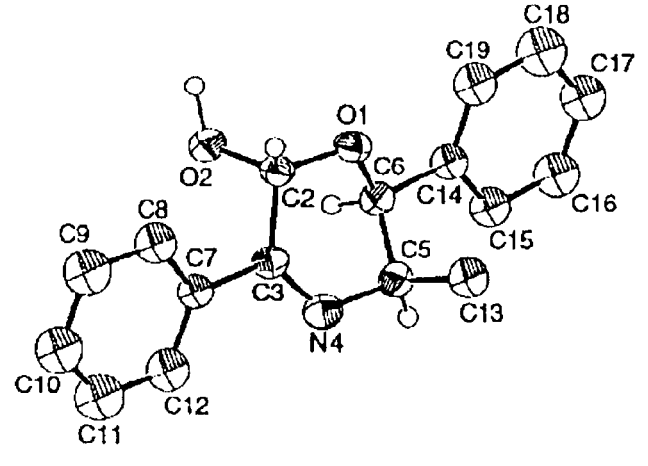


Figure 2. X-ray crystal structure of **5**.

irreversible formation of 5,6-dihydro-1,4-oxazines. Thermodynamic stability also induces the formations of **4** and **5** as single stereoisomers.

Table 1

Crystallographic Data

	4	**5**
Formula	$C_{16}H_{15}NO_2$	$C_{17}H_{17}NO_2$
Space Group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	11.997(2)	11.220(3)
b (Å)	16.997(3)	21.204(4)
c (Å)	6.353(1)	5.915(1)
V (Å^3)	1295.5(6)	1407.2(7)
z	4	4
Pcalcd (g cm^{-3})	1.30	1.26
μ (cm^{-1})	0.80 (MoKα)	6.24 (CuKα)
no. of unique reflections	1370	1271
no. of reflections with $I \geq 3\sigma_I$	1112	1098
R	0.032	0.060
Rw	0.041	0.086

Table 2

Positional Parameters for **4**

atom	x	y	z	B(eq)
O(1)	0.4630(1)	0.2379(1)	0.6107(3)	4.18(8)
O(2)	0.4324(1)	0.2728(1)	0.2605(3)	4.22(8)
N(1)	0.2137(1)	0.2626(1)	0.4115(3)	3.24(8)
C(1)	0.4138(2)	0.2921(1)	0.4715(4)	3.6(1)
C(2)	0.2886(2)	0.2957(1)	0.5237(4)	3.1(1)
C(3)	0.2448(2)	0.2208(1)	0.2173(4)	3.4(1)
C(4)	0.3704(2)	0.2051(1)	0.2003(4)	3.9(1)
C(5)	0.2557(2)	0.3443(1)	0.7082(4)	3.3(1)
C(6)	0.3328(2)	0.3696(1)	0.8565(4)	3.9(1)
C(7)	0.3001(2)	0.4160(2)	1.0235(5)	4.6(1)
C(8)	0.1907(3)	0.4381(2)	1.0463(5)	4.9(1)
C(9)	0.1140(2)	0.4140(2)	0.8988(6)	5.9(2)
C(10)	0.1459(2)	0.3680(2)	0.7308(5)	4.7(1)
C(11)	0.1838(2)	0.1437(1)	0.1963(4)	3.5(1)
C(12)	0.1382(2)	0.1217(2)	0.0047(4)	4.9(1)
C(13)	0.0908(3)	0.0479(2)	-0.0163(7)	6.9(2)
C(14)	0.0879(3)	-0.0037(2)	0.1485(8)	7.2(2)
C(15)	0.1324(3)	0.0175(2)	0.3380(6)	6.0(2)
C(16)	0.1797(2)	0.0913(2)	0.3630(5)	4.5(1)

Table 3

Selected Intramolecular Distances for **4** [8]

atom	atom	distance (A)
O(1)	C(1)	1.407(3)
O(2)	C(1)	1.398(3)
O(2)	C(4)	1.422(3)
N(1)	C(2)	1.278(3)
N(1)	C(3)	1.472(3)
C(1)	C(2)	1.539(3)
C(2)	C(5)	1.487(3)
C(3)	C(4)	1.534(3)
C(3)	C(11)	1.507(3)

EXPERIMENTAL

General.

Melting points were taken on a Thomas Hoover apparatus.

Table 4

Selected Intramolecular Bond Angles for **4** [8]

atom	atom	atom	angle(°)
C(2)	O(2)	C(4)	111.4(2)
C(2)	N(1)	C(3)	120.1(2)
O(1)	C(1)	O(2)	112.4(2)
O(1)	C(1)	C(2)	107.4(2)
O(2)	C(1)	C(2)	111.8(2)
N(1)	C(2)	C(1)	123.3(2)
N(1)	C(2)	C(5)	119.8(2)
C(1)	N(2)	C(5)	116.8(2)
N(1)	C(5)	C(4)	113.1(2)
N(1)	C(3)	C(11)	111.7(2)
C(4)	C(3)	C(11)	108.6(2)
O(2)	C(4)	C(3)	110.7(2)
C(2)	C(5)	C(6)	122.1(2)
C(2)	C(5)	C(10)	119.7(2)
C(3)	C(11)	C(12)	120.3(2)
C(3)	C(11)	C(16)	120.6(2)

Table 5

Positional Parameters for **5**

atom	x	y	z	B(eq)
O(1)	0.3893(3)	0.6020(1)	0.5477(5)	2.8(1)
O(2)	0.4145(3)	0.5020(1)	0.7007(5)	3.3(1)
C(2)	0.4646(4)	0.5486(2)	0.5636(7)	2.5(2)
C(3)	0.4905(4)	0.5189(2)	0.3342(8)	2.5(2)
N(4)	0.4436(4)	0.5367(2)	0.1500(7)	2.9(2)
C(5)	0.3572(4)	0.5891(2)	0.1536(7)	2.8(2)
C(6)	0.2973(4)	0.5941(2)	0.3827(7)	2.7(2)
C(7)	0.5776(4)	0.4657(2)	0.3362(8)	2.8(3)
C(8)	0.6620(5)	0.4596(2)	0.505(1)	3.9(1)
C(9)	0.7423(6)	0.4102(3)	0.506(1)	4.8(2)
C(10)	0.7398(5)	0.3665(2)	0.334(1)	4.7(1)
C(11)	0.6592(6)	0.3728(3)	0.165(1)	5.2(1)
C(12)	0.5778(5)	0.4224(2)	0.163(1)	4.1(1)
C(13)	0.4227(5)	0.6491(2)	0.0865(8)	3.5(2)
C(14)	0.2100(4)	0.6482(2)	0.4003(8)	3.0(1)
C(15)	0.1224(5)	0.6553(2)	0.2380(8)	3.7(2)
C(16)	0.0422(5)	0.7049(3)	0.252(1)	4.4(1)
C(17)	0.0500(5)	0.7477(3)	0.426(1)	4.5(1)
C(18)	0.1363(5)	0.7405(3)	0.588(1)	5.2(1)
C(19)	0.2160(5)	0.6909(2)	0.574(1)	4.1(1)

Table 6

Selected Intramolecular Distances for **5** [8]

atom	atom	distance (Å)
O(1)	C(2)	1.417(5)
O(1)	C(6)	1.431(5)
O(2)	C(2)	1.395(5)
C(2)	C(3)	1.523(6)
C(3)	N(4)	1.268(6)
C(3)	C(7)	1.492(6)
N(4)	C(5)	1.474(6)
C(5)	C(6)	1.516(6)
C(5)	C(13)	1.522(6)
C(6)	C(14)	1.510(6)

Table 7

Selected Intramolecular Bond Angles for **5** [8]

atom	atom	atom	angle (°)
C(2)	O(1)	C(6)	112.5(3)
O(1)	C(2)	O(2)	111.4(3)
O(1)	C(2)	C(3)	112.6(3)
O(2)	C(2)	C(3)	107.6(3)
C(2)	C(3)	N(4)	124.3(4)
C(2)	C(3)	C(7)	115.5(4)
N(4)	C(3)	C(7)	120.2(4)
C(3)	N(4)	C(5)	119.0(4)
N(4)	C(5)	C(6)	111.0(4)
N(4)	C(5)	C(13)	108.0(4)
C(6)	C(5)	C(13)	112.8(4)
O(1)	C(6)	C(5)	107.3(3)
O(1)	C(6)	C(14)	109.4(3)
C(5)	C(6)	C(14)	113.7(4)

The ir spectra were recorded on a Nicolet Impact 400 FT spectrophotometer and nmr spectra on either Bruker AMX-300 or AMX-400 spectrometers. Specific rotations were measured on a Perkin-Elmer 141 polarimeter.

(2*S*,5*R*)-5,6-Dihydro-3,5-diphenyl-2-hydroxy-1,4-oxazine (**4**).

A solution of phenylglyoxal hydrate (1.52 g, 10 mmoles) in dichloromethane (20 ml) was added to a stirred solution of (*R*)-phenylglycinol (1.37 g, 10 mmoles) in dichloromethane (30 ml) containing magnesium sulfate (3 g). The mixture was stirred vigorously for 1 hour at 0-5°, filtered and evaporated. Crystallization of the residue from ethanol afforded **4** as colorless prisms (2.2 g, 87%) mp 118°, $[\alpha]_D^{20}$ -24.0° (chloroform, c = 1); ir (Nujol): 3475 (OH) and 1640 (C=N) cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 3.79 (dd, 1H, J = 3.3 and 3.2 Hz, H-5), 4.20 (dd, 1H, J = 10.9 and 3.3 Hz, H-6a), 4.74 (dd, J = 10.9 and 3.2 Hz, H-6b) 5.29 (s, 1H, H-2), and 7.4-7.7 (m, 10H, Ph); ^{13}C nmr (75 MHz, deuteriochloroform): δ 70.1, 72.6, 83.1, 126.0, 127.5, 127.8, 128.4, 139.6, 140.1 and 175.3.

(2*R*,5*R*,6*S*)-5,6-dihydro-3,6-diphenyl-2-hydroxy-5-methyl-1,4-oxazine (**5**).

A solution of phenylglyoxal hydrate (1.52 g, 10 mmoles) in dichloromethane (20 ml) was added to a stirred solution of (1*S*,2*R*)-norephedrine (1.51 g, 10 mmoles) in dichloromethane (30 ml) containing magnesium sulfate (3 g). The mixture was stirred vigorously for 45 minutes at 0-5°, filtered and evaporated. Crystallization of the residue from chloroform-petroleum ether afforded **5** (2.43 g, 91%), mp 186°, $[\alpha]_D^{20}$ -52.0° (methanol, c = 0.5); ir (Nujol): 3490 (OH) and 1640 (C=N) cm^{-1}; ^1H nmr (400 MHz, (DMSO-d_6): δ 0.77 (d, 3H, J = 6.9 Hz, Me), 4.06 (m, 1H, H-5), 5.19 (d, 1H, J = 3.1 Hz, H-5), 5.91 (s, 1H, H-2) and 7.4-7.9 (m, 10H, Ph); ^{13}C nmr (75 MHz, (DMSO-d_6): 13.8, 55.3, 68.3, 86.7, 125.3, 126.8, 128.0, 129.8, 136.2, 139.5 and 162.2.

X-ray Crystal Structure Analysis of **4**.

Data were measured on a PW1100/20 Philips four-circle computer controlled diffractometer. MoKα (λ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by a least-squares fit of 24 centered reflections in the range of 12≤θ≤15°. Intensity data were collected using the ω-2θ technique to a maximum 2θ

of 50°. The scan width, $\Delta\omega$, for each reflection was 1.00+0.35 tanθ, with a scan speed of 3.0 deg/min. Background measurements were made for a total of 20 seconds at both limits of each scan. Three standard reflections were monitored every 60 minutes. No systematic variations in the intensities were found.

Intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were found by using the results of a SHELXS-86 direct method analysis [9]. After several cycles of refinements [10] the positions of hydrogens were calculated, and added to the refinement process. Refinement proceeded to convergence by minimizing the function $\Sigma w(|F_0|-F_c|)^2$. A final difference Fourier synthesis map showed several peaks less then 0.12 e/Å^3 scattered about the unit cell without a significant feature. The discrepancy indices, $R = \Sigma||F_0|-|F_c||/\Sigma|F_0|$ and $R_w = [\Sigma w(|F_0-F_c|)^2/\Sigma w|F_0|^2]^{1/2}$ are presented with other pertinent crystallographic data in Table 1.

X-ray Crystal Structure Analysis of **5**.

Data were measured on a ENRAF-NONIUS CAD-4 computer controlled diffractometer. CuKα (λ = 1.54178 Å) radiation with a graphite crystal monochromator in the incident beam was used. The standard CAD-4 centering, indexing, and data collection programs were used. The unit cell dimensions were obtained by a least-squares fit of 24 centered reflections in the range of $23 \leq \theta \leq 27°$. Intensity data were collected using the ω-2θ technique to a maximum 2θ of 120°. The scan width, Δθ, for each reflection was 0.80+0.35 tanθ. An aperture with a height of 4 mm and variable width, calculated as (2.0 + 0.5 tanθ) mm, was located 173 mm from the crystal. Reflections were first measured with a scan of 8.24 deg/min. The rate of the final scan was calculated from the preliminary scan results so that the ratio $I/\sigma(I)$ would be at least 40 but the maximum scan time would not exceed 60 seconds. If in a preliminary scan $I/\sigma(I) < 2$, this measurement was used as the datum. Scan rates varied from 1.27 to 8.24 deg/min. Of the 96 steps in the scan, the first and the last 16 steps were considered to be background. During data collection the intensities of the three standard reflections were monitored after every hour of x-ray exposure. No decay was observed. In addition, three orientation standards were checked after 100 reflections to check the effects of the crystal movement. If the standard deviation of the H, K, and L values of any of the orientation reflection exceeded 0.07, a new orientation matrix was calculated on the basis of the recentering of the 24 reference reflections.

Intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were found by using the results of a SHELXS-86 direct method analysis [9]. After several cycles of refinements [10] the position of hydrogens were calculated, and added to the refinement process. Refinement proceeded to convergence by minimizing the function $\Sigma w(|F_0-F_c|)^2$. A final difference Fourier synthesis map showed several peaks less then 0.3 e/Å^3 scattered about the unit cell without a significant feature. The discrepancy indices, $R = \Sigma||F_0|-|F_c||/\Sigma|F_0|$ and $Rw = [\Sigma w(|F_0-F_c|)^2/\Sigma w|F_0|^2]^{1/2}$ are presented with other pertinent crystallographic data in Table 1.

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[8] Estimated standard deviations in the least significant figure are given in parentheses.

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