Identification, Synthesis and Conformational Study of a CN(*R,S*) Synthon By-product: (5*R*, 10*R*)-5,10-Diphenyl-1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane

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The title compound, containing a new heterocyclic skeleton, was identified by X-ray crystallography as the product of condensation of (*R*)-phenylglycinol with an excess of formaldehyde. The molecule adopts a rigid double twist-chair conformation in both solid and solution states.

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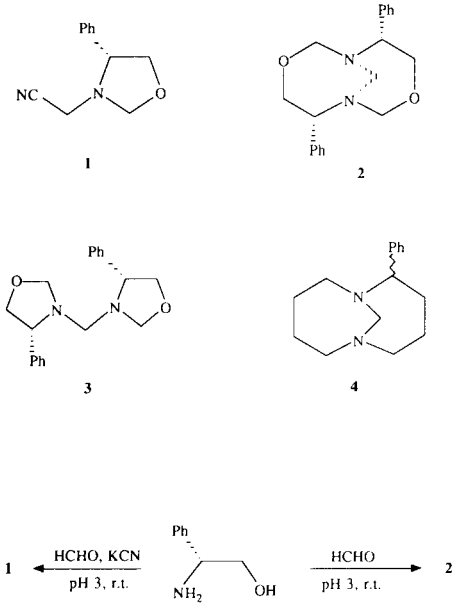
As part of an asymmetric synthesis program which we call the CN(*R,S*) method [1], we are currently exploring the use of (*R*)-*N*-cyanomethyl-4-phenyloxazolidine **1** as a chiral synthon for the preparation of amines, amino alcohols and amino acids of biological interest [2-7]. The efficient synthesis of **1**, which is routinely run on 10-30 g scale, involves condensation of (*R*)-phenylglycinol with formaldehyde in aqueous solution in the presence of cyanide ion [2]. In some runs, we have observed the formation in small quantities of a crystalline by-product. Moved principally by academic curiosity, we undertook the identification of this material.

The new product lacked a nitrile group absorbance around 2200 cm^{-1} in its ir spectrum while the presence of the monosubstituted benzene ring was confirmed by strong out-of-plane C-H deformation bands at 703 and 754 cm^{-1}. An empirical formula of $C_{19}H_{22}N_2O_2$ from combustion analysis and a molecular ion at m/e 310 in the mass spectrum suggested a product of condensation between two mole equivalents of phenylglycinol and three of

Scheme 1



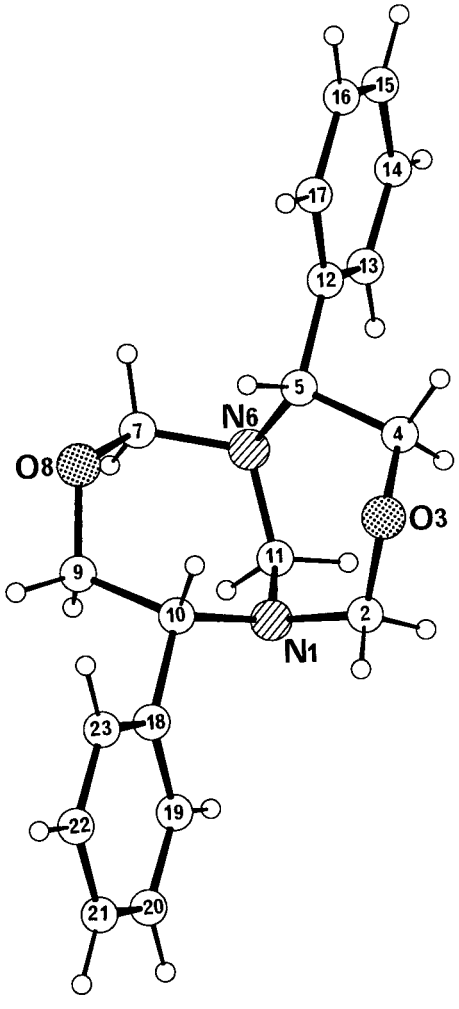


Figure 1. ORTEP diagram of **2**.

formaldehyde. 1D-Nmr spectroscopy was inconclusive in elucidating the structure (*vide infra*) and the product was finally identified unambiguously as **2** by X-ray crystallography.

With its structure in hand, the formation of **2** during the synthesis of synthon **1** can be explained by the condensation of phenylglycinol and formaldehyde when cyanide ion is not present in sufficient quantity to trap the iminium ion intermediate. Thus the synthesis of **2** in 82% yield was achieved simply by reproducing the reaction conditions for the preparation of **1**, in the complete absence of cyanide ion (Scheme 1).

The crystal structure of **2** is shown in Figure 1 with atomic labelling and the correct absolute configuration, as deduced from the known stereochemistry of the phenylglycinol precursor. Fractional coordinates (Table 1), selected bond distances and angles (Table 2) and selected torsion angles (Table 3) are listed. In the solid state **2** adopts a rigid C_2 molecular structure in which the two-fold axis lies in the N(1)-C(11)-N(6) plane, passing through C(11) and bisecting its angle. Examination of the torsion angles (Table 3) confirms the symmetry of the bicyclic skeleton, while the values define a twist-chair conformation [8] for each of the 7-membered rings in which atoms N(1) and C(4) in one ring are displaced by +0.67 and −0.78 Å respectively from the best mean plane defined by the other five atoms (maximum deviation 0.08 Å). The same observations apply for N(6) and C(9) in the second ring. Severe transannular interaction between H(5) and H(10) is reduced by considerable widening of the N(1)-C(11)-N(6) bond angle to 118° and a flattening of bridgehead nitrogen tripods which opens the *endo* face of the bi-cycle.

The symmetrical twist-chair conformation of the heterocyclic skeleton in the solid state is illustrated in Figure 2a. It seemed curious that this strained conformer should be the most stable, particularly in view of an alternative boat-boat conformation, which Dreiding molecular models suggested to be strain-free and have a considerable degree of flexibility. However, a semi-empirical molecular orbital calculation showed the energy-minimized boat-boat conformer, the heterocyclic skeleton of which is shown in Figure 2b, to be some 15 kcal/mol more energetic than the twist-chair structure.

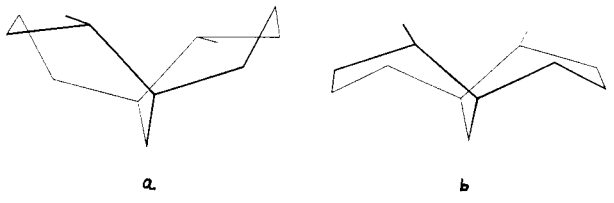


Figure 2. (a) Solid-state double twist-chair conformation of **2**, phenyl rings removed for clarity. (b) Disfavored alternative double boat conformation.

Table 1

Fractional Coordinates (x10^4) for the Non-hydrogen Atoms, (x10^3) for the Hydrogen Atoms and the Equivalent Ueq (Å^2 x10^3) Isotropic Thermal Factor

	X	Y	Z	Ueq
N1	-206 (4)	1063 (10)	1464 (3)	54 (4)
C2	638 (5)	-434 (13)	1161 (5)	63 (5)
O3	1403 (3)	-1601 (10)	2080 (3)	67 (4)
C4	2183 (5)	-179 (14)	2867 (5)	65 (6)
C5	1602 (5)	937 (12)	3727 (4)	53 (5)
N6	811 (4)	2808 (11)	3284 (4)	59 (4)
C7	-91 (6)	3142 (14)	3906 (5)	69 (6)
O8	-967 (3)	1406 (11)	3769 (3)	69 (4)
C9	-1710 (5)	1180 (14)	2664 (4)	62 (5)
C10	-1135 (5)	-160 (11)	1869 (4)	55 (5)
C11	340 (5)	3007 (12)	2072 (5)	62 (5)
C12	2606 (5)	1704 (13)	4720 (4)	56 (5)
C13	3179 (6)	3727 (14)	4706 (6)	72 (6)
C14	4130 (7)	4378 (16)	5605 (7)	90 (8)
C15	4498 (6)	2939 (17)	6516 (6)	81 (7)
C16	3951 (5)	928 (16)	6535 (5)	75 (7)
C17	2999 (5)	295 (14)	5639 (5)	64 (5)
C18	-2126 (4)	-986 (11)	881 (4)	54 (5)
C19	-2448 (5)	164 (15)	-123 (5)	70 (6)
C20	-3368 (6)	-613 (17)	-994 (6)	82 (7)
C21	-3969 (6)	-2527 (17)	-882 (7)	85 (8)
C22	-3663 (6)	-3682 (16)	114 (7)	97 (9)
C23	-2735 (6)	-2941 (13)	996 (6)	78 (7)
H2a	16 (5)	-177 (11)	59 (5)	70
H2b	125 (5)	77 (12)	94 (5)	70
H4a	280 (5)	-128 (12)	324 (5)	70
H4b	246 (5)	104 (12)	251 (5)	70
H5	108 (5)	-39 (11)	382 (5)	58
H7a	30 (6)	324 (13)	472 (5)	77
H7b	-56 (5)	454 (13)	358 (6)	77
H9a	-254 (5)	43 (12)	268 (5)	70
H9b	-199 (5)	269 (13)	236 (5)	70
H10	-82 (4)	-164 (12)	231 (4)	60
H11a	-22 (5)	433 (12)	200 (5)	67
H11b	100 (5)	363 (11)	179 (5)	67
H13	291	474	404	80
H14	454	585	559	100
H15	517	339	717	90
H16	423	-10	719	83
H17	260	-118	566	71
H19	-201	156	-22	77
H20	-360	25	-171	90
H21	-463	-308	-152	95
H22	-411	-507	21	106
H23	-250	-382	171	88

Although we were unable to deduce the structure of **2** by nmr - the 1D data could be equally well attributed to the alternative structure **3** for example - the technique was useful in studying its solution state behavior once its structure was established. In dilute benzene-d_6 solution, a single set of carbon resonances is observed and the six aliphatic protons of the symmetrical half structure are completely resolved in the ^{1}H nmr spectrum. J-modulation [9]

Table 2

Selected Bond Distances (Å) and Angles (°)

N1 - C2	1.438 (8)	C16 - C17	1.396 (8)
N1 - C10	1.481 (7)	C18 - C19	1.379 (9)
N1 - C11	1.437 (9)	C18 - C23	1.387 (10)
C2 - O3	1.427 (8)	C19 - C20	1.384 (10)
O3 - C4	1.423 (9)	C20 - C21	1.361 (13)
C4 - C5	1.539 (9)	C21 - C22	1.372 (13)
C5 - N6	1.458 (9)	C22 - C23	1.389 (11)
C5 - C12	1.526 (8)	C2 - H2a	1.12 (7)
N6 - C7	1.452 (8)	C2 - H2b	1.08 (6)
N6 - C11	1.456 (7)	C4 - H4a	.99 (7)
C7 - O8	1.428 (9)	C4 - H4b	.95 (7)
O8 - C9	1.418 (6)	C5 - H5	1.02 (6)
C9 - C10	1.537 (8)	C7 - H7a	.99 (7)
C10 - C18	1.525 (7)	C7 - H7b	1.02 (7)
C12 - C13	1.379 (11)	C9 - H9a	1.06 (6)
C12 - C17	1.390 (9)	C9 - H9b	1.00 (7)
C13 - C14	1.401 (11)	C10 - H10	1.05 (7)
C14 - C15	1.390 (12)	C11 - H11a	1.01 (7)
C15 - C16	1.360 (13)	C11 - H11b	.98 (7)

C2	N1	C10	112.0 (5)
C2	N1	C11	113.6 (5)
C10	N1	C11	118.9 (5)
N1	C2	O3	115.0 (5)
C2	O3	C4	113.9 (5)
O3	C4	C5	114.6 (5)
C4	C5	N6	114.5 (5)
C4	C5	C12	107.8 (5)
N6	C5	C12	110.3 (5)
C5	N6	C7	111.9 (5)
C5	N6	C11	118.8 (5)
C7	N6	C11	113.3 (5)
N6	C7	O8	114.7 (6)
C7	O8	C9	114.9 (5)
O8	C9	C10	113.9 (5)
N1	C10	C9	114.9 (5)
N1	C10	C18	110.6 (5)
C9	C10	C18	108.5 (5)
N1	C11	N6	117.9 (5)
C5	C12	C13	121.5 (6)
C5	C12	C17	119.7 (5)
C13	C12	C17	118.8 (6)
C12	C13	C14	121.0 (7)
C13	C14	C15	118.9 (8)
C14	C15	C16	120.7 (8)
C15	C16	C17	120.1 (7)
C12	C17	C16	120.5 (6)
C10	C18	C19	122.0 (5)
C10	C18	C23	119.2 (5)
C19	C18	C23	118.7 (6)
C18	C19	C20	120.4 (7)
C19	C20	C21	120.9 (7)
C20	C21	C22	119.3 (8)
C21	C22	C23	120.7 (8)
C18	C23	C22	119.9 (7)

and heteronuclear correlation [10] experiments permit identification of carbon and proton signals as shown in Figure 3.

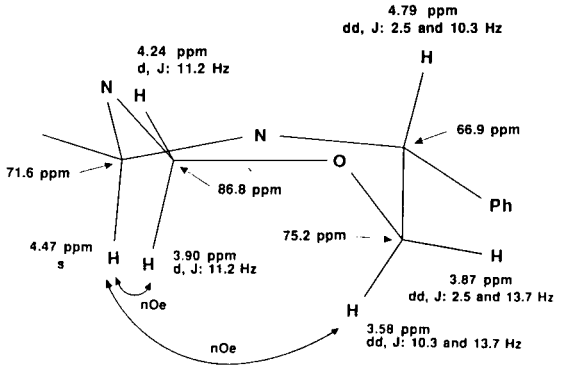


Figure 3. Half-structure of **2** in twist-chair form showing the five-atom plane, nmr signal attributions and observed nOe.

Table 3

Selected Torsion Angles (°)

C11	N1	C2	O3				69.7 (6)
N1	C2	O3	C4				-63.9 (6)
C2	O3	C4	C5				81.4 (6)
O3	C4	C5	N6				-76.2 (6)
C4	C5	N6	C11				19.3 (5)
C5	N6	C11	N1				49.9 (5)
N6	C11	N1	C2				-84.7 (6)
C11	N6	C7	O8				69.2 (6)
N6	C7	O8	C9				-64.6 (6)
C7	O8	C9	C10				81.4 (6)
O8	C9	C10	N1				-75.4 (6)
C9	C10	N1	C11				18.9 (5)
C10	N1	C11	N6				50.3 (5)
N1	C11	N6	C7				-84.5 (6)
O3	C4	C5	C12				160.7 (7)
C4	C5	C12	C13				84.2 (7)
C7	N6	C5	C12				-83.9 (6)
N6	C5	C12	C13				-41.5 (6)
O8	C9	C10	C18				160.2 (7)
C9	C10	C18	C19				95.7 (6)
C2	N1	C10	C18				-82.2 (6)
N1	C10	C18	C19				-31.2 (5)
H4a	C4	C5	H5				-76 (5)
H4b	C4	C5	H5				159 (5)
H9a	C9	C10	H10				-74 (4)
H9a	C9	C10	H10				176 (5)

The observation of a strong nOe between the H(11) singlet and one of the H(2) doublets in a NOESY [11] experiment can be explained only by the twist-chair conformation in which the affected proton is the axial $H(2)_{exo}$. In the boat conformation, this proton would be equatorial and neither it nor $H(2)_{endo}$ would be likely to experience an nOe. A small nOe is observed between H(11) and one of the H(4) double doublets which identifies the latter as $H(4)_{exo}$, although not distinguishing boat and twist-chair conformations. With all protons now identified, the coupling constants for the $H(4)_{exo}$:$H(4)_{endo}$:H(5) system are nice-

ly rationalized by the twist-chair conformation. In particular the $H(4)_{endo}$-C(4)-C(5)-H(5) torsion angle of 76° accounts for the small $^{1,3}J$ value of 2.5 Hz between $H(4)_{endo}$ and H(5).

The conformation of **2** in chloroform solution is less well defined. In dilute deuteriochloroform solution, the ^1H nmr spectrum is abnormally simple, even for the symmetrical half-structure, showing a singlet for two H(2) protons at δ 4.21 ppm, a doublet for two H(4) protons at 3.97 ppm apparently coupled (J = 6.5 Hz) with the one-proton triplet of H(5) at δ 4.62 ppm as well as the H(11) singlet at δ 4.86 ppm. The apparent equivalence of the geminal protons on both prochiral methylene groups is more likely due to a deceptively simple ABX spectral system than an averaging of signals from two or more conformers, for a temperature dependent study showed no change in the deuteriochloroform solution ^1H and ^{13}C spectrum over the range −50° to 50°. The dilute deuteriochloroform solution ^{13}C nmr spectrum is virtually identical to that observed in benzene-d_6, but in concentrated solutions (above 100 mg/ml) a phenomenon is observed which we attribute to aggregation whereby the ^{13}C nmr spectrum displays a major and minor set of resonances. This second set of peaks disappears on dilution of the sample.

The significance of the solvent in determining physical behavior is highlighted by the large difference in optical rotations recorded for **2** in benzene (−209°) and in chloroform (−156°) at similar concentrations.

We note that there is no evidence for the formation of **3** from formaldehyde and phenylglycinol. While the condensation of a β-aminoalcohol with a carbonyl compound *via* an imino species to give an oxazolidine is well documented [12], and is indeed probably the mechanism through which synthon **1** is formed, Baldwin's rules [13] appear to be respected in the present case, in which a 7-*endo-trig* cyclization is favoured over a 5-*endo-trig* process. Neither does **2** isomerize to **3** in solution: the chloroform-solution ir spectrum of **2** is identical with that recorded for the solid state, while nmr experiments provide no evidence for a second solution state structure (with the exception of the aggregation effect in concentrated deuteriochloroform solution) nor for an open-chain imine, the only plausible intermediate for an isomerization process [14]. In any case, ring-chain tautomerism of 7-membered rings is a rare occurence [15].

To the best of our knowledge, the 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane skeleton is unprecidented in the literature, and its non-oxygenated parent 1,6-diazabicyclo-[4.4.1]undecane has been reported on only a few occasions [16-20]. Claims of central nervous system stimulant activity of the 2-aryl derivative **4** in the patent literature [19-20] attracted our attention, but pursuit of pharmacological studies of **2** is limited by its acid sensitivity. Treatment with hydrochloric acid in methanol in an effort to generate a water soluble hydrochloride results predictably in its immediate hydrolysis to give phenylglycinol.

EXPERIMENTAL

Melting point determination was performed without correction using a Reichert Thermovar apparatus. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Electronic ionization mass spectra were recorded on an MS 50 instrument. Elemental analysis was carried out by the microanalytical service laboratory in the ICSN. Infrared spectra were recorded in a potassium bromide disc or in chloroform solution on a Nicolet 205 FT-IR spectrometer. The nmr spectra were recorded on a Bruker AC 200, with the exception of the variable temperature experiments, which were carried out on a Bruker AC 300. Data were manipulated using standard Bruker software. Chemical shifts were measured relative to internal solvent residues and are expressed in ppm relative to tetramethylsilane. For the NOESY experiments mixing times of 250 or 300 milliseconds were used. Semi-empirical molecular orbital calculations were carried out using the program MOPAC [21].

Synthesis of (5*R*,10*R*)-5,10-Diphenyl-1,6-diaza-3,8-dioxabicyclo-[4.4.1]undecane **2**.

A solution of (*R*)-phenylglycinol (2.50 g, 18.2 mmoles) in water (25 ml) was adjusted to *p*H 3 by addition of solid citric acid. The mixture was stirred at room temperature while formaldehyde (37% w/v solution in water, 10 ml, 123.2 mmoles) was added dropwise over 30 minutes. After a further 3 hours the mixture was made slightly alkaline by addition of solid sodium carbonate, then set aside at 0° overnight. The resulting white precipitate was collected by filtration, washed with water, then dried *in vacuo*. Crystallization from benzene-heptane gave 2.31 g (82%) of white needles, mp 135-168°: this long melting range, accompanied by decomposition, persisted even after repeated crystallization; $[\alpha]_D^{23} = -209°$ (c 1.23, benzene), −156° (c 1.72, chloroform); ms: m/e 310 (M^+, 11), 280 (100), 250 (33), 206 (9), 176 (6), 162 (93), 132 (21), 118 (64), 104 (47), 91 (76); ir: ν 703, 754, 1009, 1094, 1236, 1329, 1450, 1479, 1602w, 2864, 2909, 2958, 3029w, 3055w cm^{-1}; ^1H nmr (benzene-d_6): δ 3.58 (1H, dd, J 10.3 and 13.7 Hz), 3.87 (1H, dd, J 2.5 and 13.7 Hz), 3.90 (1H, d, J 11.2 Hz), 4.24 (1H, d, J 11.2 Hz), 4.47 (1H, s), 4.79 (1H, dd, J 10.3 and 2.5 Hz), 7.1-7.3 (5H, m); ^{13}C nmr (benzene-d_6): δ 66.9, 71.6, 75.2, 86.8, 128.0, 128.3, 129.1, 142.8.

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.27; H, 6.75; N, 9.05.

X-ray Study.

Small crystals grown by partial evaporation of a chloroform solution belonged to the monoclinic system, space group $P2_1$. Cell parameters: a = 11.531(8), b = 5.971(5), c = 12.291(8) Å; β = 104.59(2)°; V = 819.0 Å^3; Z = 2; one molecule per asymmetric unit. D_{cal} = 1.26 g cm^{-3}, F(000) = 332. A small crystal (approximate dimensions 0.15 x 0.25 x 0.4 mm) was mounted on a Philips PW 1100 diffractometer and data were collected using graphite monochromated Cu K_α radiation:λ(Cu K_α) = 1.5418 Å, μ = 5.7 cm^{-1} (absorption ignored). From the 2625 reflections measured (h:0 → ±13, k:0 → 6, l:0 → 14) by the θ-2θ scan technique up to θ = 65°, 1464 were unique (R_{int} = 0.067) of which 1256 were considered as observed having $I \geq 2.5\sigma(I)$ [σ(I) from counting statistics] and were kept in refinement calculations. The

structure was solved by direct methods using program SHELXS86 [22] and refined anisotropically by full-matrix least-squares minimizing of the function $\Sigma w(| F_o | - | F_c |)^2$, where $w = [\sigma^2(F_o) + 0.006523F_o^2]^{-1/2}$, using the program SHELX76 [23]. All the hydrogen atoms were located on successive difference Fourier maps. Those bonded to atoms of the heterocyclic skeleton were retained in their experimental positions for refinement while those bonded to phenyl rings were introduced in the refinement at theoretical positions (d_{C-H} = 1.00 Å). All hydrogen atoms were assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.066, wR = 0.097 (with $wR = \{\Sigma w(| F_o | - | F_c |)^2/\Sigma wF_o^2\}^{1/2}$, G_{fit} = 1.018). Maximum shift/esd ratio in the final cycle was 0.24, and no residue higher than 0.19 e Å^{-3} was observed in the final difference Fourier map.

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