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Molecular Structure and Conformation of the (Z) and (E) Geometric Isomers of 2-(2-phenylbenzylidene)-3 Quinuclidinone

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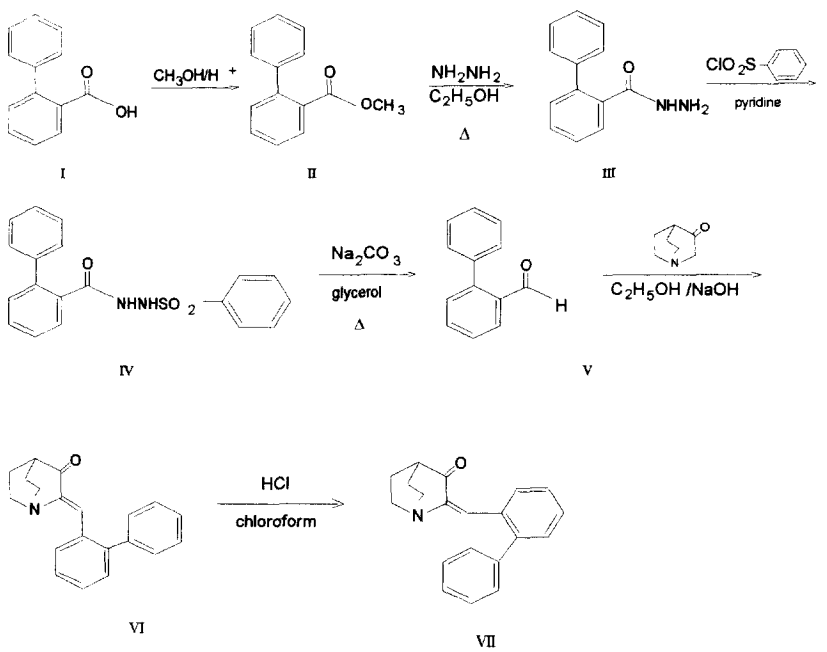
Abstract: The crystal structures of the (Z) and (E) geometric isomers of 2-(2-phenylbenzylidene)-3-quinuclidinone were solved by direct methods, using diffractometric data, and refined to final R values of 0.040 and 0.061. The molecules of the (Z) and (E) geometric isomers show *trans* and *cis* conformation of the substituents around the double bond, respectively. The quinuclidine and the diphenyl moieties show deformations in their geometric and conformational parameters due to the need of releasing intramolecular strains and/or non-bonded interactions.

INTRODUCTION

Substance P is a peptide neurotransmitter that binds to the NK-1 receptor and is involved in pain transmission and neurogenic inflammation[1-4]. Recently, the non-peptide substance P antagonist CP-96,345 (Figure 1) has been shown to be effective in animal models of pain and inflammation[5-6]. We have already described the synthesis of various quinuclidines structurally related to CP-96,345 and their evaluation in binding assays on NK-1, NK-2 and NK-3 receptor subtypes[7]. In the course of the preparation of the above mentioned 2-benzylidene- and 2-benzyl-3-benzylamino quinuclidines, we had to prepare the (Z)- and (E)-2-(2-phenylbenzylidene)-3-quinuclidinones as intermediates (VI and VII in Figure 1). Here we report the X-ray crystal stucture determination with confirmation of the configuration assignement for the double bond for both isomeric species. The synthesis of (Z) and (E) molecules **(VI)** and **(VII)**, respectively, is outlined in Scheme 1.

EXPERIMENTAL

Synthesis of (Z)- and (E)-2-(2-phenylbenzylidene)3-quinuclidinones.



Scheme 1

2-Phenylbenzoic acid (**I**) was the starting material. It was treated with methanol saturated with gaseous HCl to gave methyl 2-phenylbenzoate (**II**). Reaction of this ester with hydrazine monohydrate in warm ethanol gave 2-phenylbenzoylhydrazine (**III**). Treatment of (**III**) with benzenesulfonylchloride in pyridine medium furnished the sulphonylhydrazine (**IV**), which was successively treated with anhydrous sodium carbonate and glycerol according to the procedure of McFadyen and Stevens[8] to give the 2-phenylbenzaldehyde (**V**).

The single isomer (Z)-2-(2-phenylbenzylidene)-3-quinuclidinone (**VI**) was obtained in satisfactory yields by reaction of the aldehyde (**V**) with 3-quinuclidinone in the presence of sodium hydroxyde as catalyst. Compound (**VI**) was converted in quantitative yields, by dissolution in chloroform and treatment with anhydrous HCl gas for a few minutes, into the required hydrochloride salt (**VII**) (E- configuration at the double bond) which was crystallized from absolute ethanol.

X-Ray diffraction analysis of (Z)- and (E)-2-(2-phenylbenzylidene)3-quinuclidinones.

Single crystals of the (Z) and (E) geometric isomers of 2-(2-phenylbenzylidene)-3-quinuclidinone were obtained from methanol/water (1:1) mixtures. Preliminary oscillation and Weissenberg photographs were taken to establish the crystal symmetry and the space group. Determination of the cell constants and collection of the

X-ray intensity data were performed on an automated four-circle CAD4 Enraf-Nonius single crystal X-ray diffractometer. Unit cell parameters were obtained by a least-squares procedure on the angular parameters of 25 reflections in the range 17-22°, using the graphite monochromated, Nickel filtered, CuK_{α} radiation. Crystal data and some details of experimental results are given in Table I.

Table I. Crystal Data for (Z)-2-(2-phenilbenzylidene)-3-quinuclidinone (VI) and (E)-2-(2-phenilbenzylidene)-3-quinuclidinone (VII).

Molecule	(VI)	(VII)
Molecular Formula	$C_{20}H_{30}NO$	$C_{20}H_{19}NO \cdot HCl \cdot H_2O$
Formula weight, D	300.47	324.83
Crystal system	monoclinic	triclinic
Dimensions, mm	0.3·0.2·0.3	0.2·0.2·0.4
Space Group	$P2_1/c$	P1
Z, molecules/cell	4	4
a, Å	6.9809(4)	8.4432(2)
b, Å	19.052(3)	13.841(3)
c, Å	11.773(4)	16.313(2)
α, deg	90.000(2)	82.106(5)
β, deg	100.92(3)	101.93(6)
γ, deg	90.000(2)	99.621(6)
V, $Å^3$	1537.5(3)	1825.5(5)
d (exp.), g/cm^3	1.29	1.18
d (calc.), g/cm^3	1.298	1.182
h index range, min/max	-8/8	-10/10
k index range, min/max	0/23	-16/16
l index range, min/max	0/14	0/19
Radiation, Å	Cu Kα (λ=1.54184, Ni filtered)	Cu Kα (λ=1.54184, Ni filtered)
Solvent	CH_3OH/H_2O 1:1	CH_3OH/H_2O 1:1
Temperature, °C	22	22
R	0.040	0.061
R_w	0.037	0.061
Standard deviations of observation of unit weight	0.554	0.937
Residue electronic density max./min. $\Delta F(e/Å^3)$	+0.17/-0.17	+0.50/-0.42

The analysis of the peak profiles suggested an ω-2θ scan mode for the both data collections, with a scan angle equal to $(1.0\pm0.15 \tan \Theta)°$; backgrounds counts were taken in an additional area of $\Delta\omega/4$ on both sides of the main scan with the same scan speed for each reflections.

Data were collected up to 70° in θ, at a 295K temperature. A crystal-to-counter distance of 368 mm was used with counter entrance aperture of 4 mm.

The tube placed between the goniometer head and the detector was evacuated using an oil pump. Prescan runs were made at a speed of 3.5°/min.

Reflections with a net intensity $I<0.5\sigma(I)$ were flagged as "weak"; those having $I\geq0.5\sigma(I)$ were measured at a lower speed (1.0÷3.5°/min) depending on the value of $\sigma(I)/I$.

Three intensity control reflections were measured every 60 min of X-ray exposure time in order to monitor the crystal and the electronic stability; no significant change in intensity was observed during data collection.

Orientation matrix checks were made with respect to the scattering vectors of four well centered reflections every 200 reflections measured; re-orientation procedure was made by using 25 high-angle reflections, if the displacements of the measured scattering vector exceeded the calculated value by 0.15°, but never used.

All reflections were corrected for Lorentz and polarization effects[9]. For the molecules (**VI**) and (**VII**), 3163 and 6922 independent reflections, respectively, were collected.

The structure of (**VI**) was solved by direct methods as programmed in MULTAN[10]. The solution with the best figure of merit revealed the coordinates of most of the non-hydrogen atoms; the remaining ones were recovered from subsequent difference Fourier maps.

The structure of (**VII**), with two independent quinuclidinone molecules, two molecules of chloridric acid and two water molecules in the asymmetric unit, was solved by direct methods, as programmed in SIR92[11].

In this case the atomic positions of the entire molecules were determined using a recycling procedure using the atomic coordinates of partial fragments determined analyzing the E-map obtained with the best set of phases.

For the refinement, in both cases, the SDP (Structure Determination Programs) package[12, 13] and a full-matrix least-squares procedure was used[12], minimizing the quantity $\Sigma w(F_o^2-F_c^2)^2$, with a weight w equal to $1/\sigma(F_o^2)$.

The reflections considered "observed" and used in the refinement were 2645 and 6240 [with $F_o>3.0\ \sigma(F_o)$], for molecule (Z) and (E), respectively.

All non hydrogen atoms were refined with anisotropic temperature factors. Hydrogen atoms were located by difference Fourier techniques and included in the structure factors calculation with a B_{eq} thermal parameter equal to that of the corresponding carrier atom, but non refined.

Refinement was ended when the shifts in the atomic coordinates and temperature factors for the non-hydrogen atoms were less than 1/5 and 1/3 of the corresponding standard deviations, respectively.

The atomic scattering factors, with the real and imaginary dispersion corrections for all atomic species, were calculated according to Cromer and Waber[9].

The final R index for was 0.040 (R_w=0.037) and 0.061 (R_w=0.061) for (**VI**) and (**VII**) molecules, respectively.

All calculations were performed on a VAX3100 Digital computer (running under VMS) of the "Centro di Biocristallografia del C.N.R." at the University of Naples "Federico II".

RESULTS AND DISCUSSION

X-ray diffraction analyses of (Z)-2-(2-phenilbenzylidene)-3-quinuclidinone (**VI**) and (E)-2-(2-phenilbenzylidene)-3-quinuclidinone (**VII**) were prompted because of the need of establishing the configuration of the double bond in the two derivatives, since they are key intermediates in the preparation of new non-peptidic analogs active on the NK-1 receptors.

The geometric isomers of the 2-(2-phenilbenzylidene)-3-quinuclidinone molecule are characterized by a double bond between the C2 and C9 carbon atoms (Figure 1), existing then as (Z) or (E) isomer, according to the synthetic procedure used.

Figure 4 clearly shows by the superposition of the two independent molecules of the (E) isomer that the two molecules are practically identical. Atomic coordinates and relevant torsion angles are listed in Table II and III for the (Z) isomer and in Tables IV and V for the (E) isomer.

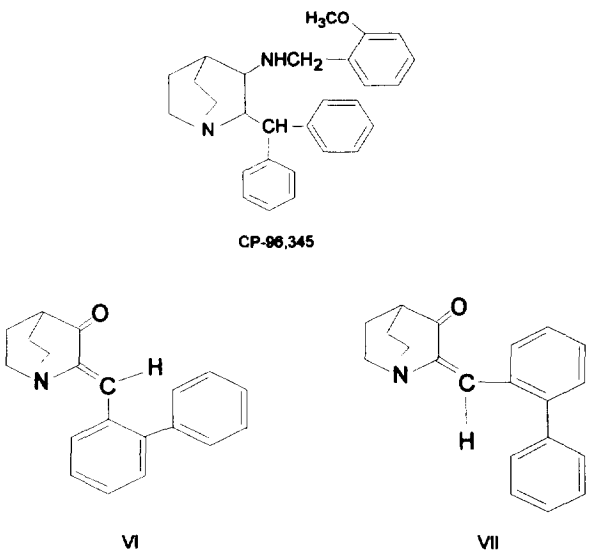


Fig. 1. The non-peptidic substance P antagonist CP-96,345 and the molecules studied: (Z)- and (E)-2-(2-phenylbenzylidene)-3-quinuclidinones (VI) and (VII).

Preliminary results on the geometry and conformation of the (Z) isomer have been recently reported by us[14]. The structure and conformation of the (E) isomer is now described and compared in details to that observed for the (Z) derivative.

The molecular models of the (Z) and of the two independent molecules of the (E) isomers, obtained by PLUTO[15], with the numbering scheme of the atoms are represented in Figure 2. Stereo drawings plots for the two isomers are shown in Figure 3.

For the (E) isomers both independent molecules present in the asymmetric unit are shown, while the co-crystallized water and hydrochloric acid molecules are not indicated.

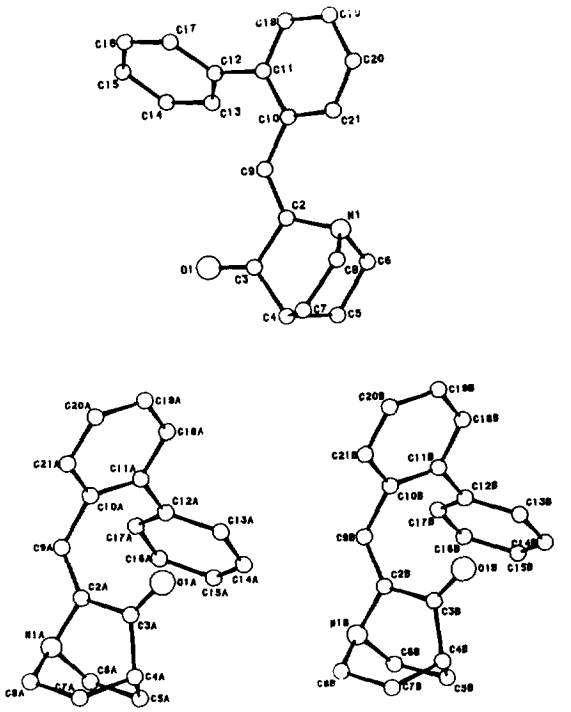


Fig. 2. Molecular models of (Z), upper part, and of the monohydrate chloridrate of the (E)-2-(2-phenyl benzylidene) -3- quinuclidinone (two indipendent molecules), lower part; with the numbering of the atoms.

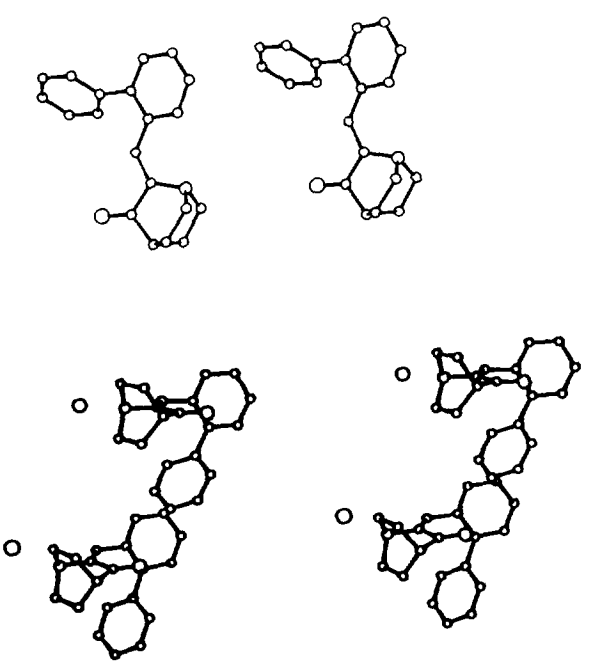


Fig. 3. Stereo plots of (Z), upper part, and of the monohydrate chloridrate of the (E)-2-(2-phenylbenzylidene)-3-quinuclidinone, lower part. In the latter each chlorine ion is shown as an open circle.

Table II. Fractional Coordinates (Å) for the Molecule of (Z)-2-(2-phenilbenzylidene)-3-quinuclidinone (VI); Estimated Standard Deviation in Parentheses.

	x/a	y/b	z/c	B(eq)
N1	0.9077 (1)	0.1630 (0)	0.0789 (1)	3.39(3)
O1	0.5474 (1)	0.2673 (0)	0.1846 (1)	4.99(3)
C2	0.7355 (2)	0.1718 (0)	0.1294 (1)	2.94(3)
C3	0.6833 (2)	0.2467 (0)	0.1420 (1)	3.41(3)
C4	0.8206 (2)	0.2944 (0)	0.0928 (1)	3.95(4)
C5	1.0273 (2)	0.2796 (1)	0.1601 (1)	4.93(5)
C6	1.0714 (2)	0.2008 (1)	0.1518 (1)	4.76(5)
C7	0.8088 (3)	0.2727 (1)	-0.0334 (1)	4.57(4)
C8	0.8704 (2)	0.1956 (1)	-0.0363 (1)	4.10(4)
C9	0.6269 (2)	0.1199 (0)	0.1601 (1)	2.96(3)
C10	0.6472 (2)	0.0440 (0)	0.1508 (1)	2.85(3)
C11	0.5461 (2)	-0.0016 (0)	0.2138 (1)	2.97(3)
C12	0.4202 (2)	0.0241 (0)	0.2934 (1)	3.17(3)
C13	0.4862 (2)	0.0694 (1)	0.3847 (1)	3.83(4)
C14	0.3661 (3)	0.0906 (1)	0.4595 (1)	4.74(4)
C15	0.1759 (2)	0.0662 (1)	0.4433 (1)	4.91(4)
C16	0.1081 (2)	0.0215 (1)	0.3538 (1)	4.98(5)
C17	0.2273 (2)	0.0000 (1)	0.2787 (1)	4.08(4)
C18	0.5613 (2)	-0.0740 (0)	0.1991 (1)	3.52(4)
C19	0.6690 (2)	-0.1016 (0)	0.1232 (1)	3.85(4)
C20	0.7664 (2)	-0.0573 (0)	0.0600 (1)	3.73(4)
C21	0.7560 (2)	0.0141 (0)	0.0742 (1)	3.37(3)

Definition of B(eq.):

$B(eq) = 4/3 \cdot [\, a^2 \cdot B_{11} + b^2 \cdot B_{22} + c^2 \cdot B_{33} + a \cdot b \cdot \cos(\gamma) \cdot B_{12} + a \cdot c \cdot \cos(\beta) \cdot B_{13} + b \cdot c \cdot \cos(\alpha) \cdot B_{23} \,]$

Table III. Torsion Angles (deg) for (Z)-2-(2-phenilbenzylidene)-3-quinuclidinone (VI); Estimated Standard Deviation in Parentheses.

O1 -C3 -C2 -N1	-178·2(3)	C8 -C7 -C4 -C3	-59·7(2)
C4 -C3 -C2 -N1	2·7(2)	C8 -C7 -C4 -C5	55·6(3)
C4 -C5 -C6 -N1	2·1(2)	C9 -C2 -N1 -C6	-124·3(3)
C4 -C7 -C8 -N1	4·4(2)	C9 -C2 -N1 -C8	118·6(3)
C5 -C4 -C3 -O1	121·3(3)	C9 -C2 -C3 -O1	3·4(3)
C5 -C4 -C3 -C2	-59·6(2)	C9 -C2 -C3 -C4	-175·7(3)
C5 -C6 -N1 -C2	-59·5(3)	C10 -C9 -C2 -N1	-0·9(3)
C6 -N1 -C2 -C3	57·3(2)	C10 -C9 -C2 -C3	177·3(4)
C6 -C5 -C4 -C3	55·8(3)	C11 -C10 -C9 -C2	164·4(3)
C7 -C4 -C3 -O1	-122·2(3)	C12 -C11 -C10 -C9	-1·5(2)
C7 -C4 -C3 -C2	56·9(2)	C13 -C12 -C11 -C10	-55·7(3)
C7 -C4 -C5 -C6	-59·3(3)	C14 -C13 -C12 -C11	-178·0(4)
C7 -C8 -N1 -C2	55·3(2)	C15 -C14 -C13 -C12	0·0(3)
C7 -C8 -N1 -C6	-62·0(3)	C15 -C16 -C17 -C12	-0·2(3)
C8 -N1 -C2 -C3	-59·8(2)	C16 -C15 -C14 -C13	0·0(3)
C8 -N1 -C6 -C5	57·7(2)	C16 -C17 -C12 -C11	178·2(4)
C16 -C17 -C12 -C13	0·2(3)	C17 -C12 -C11 -C10	126·4(3)
C17 -C12 -C13 -C14	-0·1(3)	C17 -C16 -C15 -C14	0·1(3)
C18 -C11 -C10 -C9	177·1(3)	C18 -C11 -C12 -C13	125·7(3)
C18 -C11 -C12 -C17	-52·2(3)	C19 -C18 -C11 -C10	-1·3(3)

C19 -C18 -C11 -C12	177·3(3)	C19 -C20 -C21 -C10	-0·6(3)
C20 -C19 -C18 -C11	0·5(3)	C20 -C21 -C10 -C9	-176·1(3)
C20 -C21 -C10 -C11	-0·2(3)	C21 -C10 -C9 -C2	-19·8(3)
C21 -C10 -C11 -C12	-177·4(3)	C21 -C10 -C11 -C18	1·2(2)
C21 -C20 -C19 -C18	0·5(3)		

Table IV.Fractional Coordinates (Å) for the two Independent Molecules of (E)-2-(2-phenilbenzylidene)-3-quinuclidinone (VII), Labelled A and B; Estimated Standard Deviation in Parentheses.

	x/a	y/b	z/c	B(eq)
N1	0.4113 (2)	0.1132 (1)	0.1344 (1)	3.57(5)
O1A	0.4848 (2)	0.3602 (1)	0.1896 (1)	4.72(5)
ClA	0.8379 (1)	-0.0030 (0)	0.1035 (0)	6.70(2)
C2A	0.3582 (3)	0.1998 (1)	0.1581 (1)	3.22(5)
C3A	0.4954 (3)	0.2808 (2)	0.1708 (1)	3.46(6)
C4A	0.6519 (3)	0.2499 (2)	0.1584 (2)	4.38(7)
C5A	0.6211 (4)	0.2237 (2)	0.0682 (2)	5.44(8)
C6A	0.4793 (3)	0.1409 (2)	0.0543 (1)	4.67(7)
C7A	0.6839 (3)	0.1580 (2)	0.2205 (2)	5.01(8)
C8A	0.5409 (3)	0.0756 (2)	0.2042 (2)	4.55(7)
C9A	0.2030 (3)	0.1963 (2)	0.1675 (1)	3.60(6)
C10A	0.1370 (3)	0.2814 (2)	0.1871 (1)	3.41(6)
C11A	0.1130 (3)	0.3631 (2)	0.1274 (1)	3.36(6)
C12A	0.1486 (3)	0.3661 (2)	0.0414 (1)	3.52(6)
C13A	0.2564 (3)	0.4439 (2)	0.0112 (2)	4.34(7)
C14A	0.2956 (3)	0.4448 (2)	-0.0676 (2)	5.13(8)
C15A	0.2276 (3)	0.3715 (3)	-0.1170 (2)	5.35(8)
C16A	0.1179 (4)	0.2942 (2)	-0.0887 (2)	5.39(9)
C17A	0.0797 (3)	0.2922 (2)	-0.0095 (2)	4.46(7)
C18A	0.0588 (3)	0.4430 (2)	0.1507 (2)	4.01(6)
C19A	0.0274 (3)	0.4422 (2)	0.2307 (2)	4.52(7)
C20A	0.0490 (3)	0.3609 (2)	0.2881 (2)	4.66(7)
C21A	0.1018 (3)	0.2802 (2)	0.2668 (1)	4.22(7)
N1B	-0.0430 (2)	0.1126 (1)	-0.3834 (1)	3.76(5)
O1B	0.0312 (2)	0.3526 (1)	-0.3141 (1)	4.72(5)
ClB	-0.2817 (1)	-0.0743 (0)	-0.3943 (0)	6.02(2)
C2B	-0.0937 (3)	0.1933 (1)	-0.3497 (1)	3.29(6)
C3B	0.0385 (3)	0.2781 (2)	-0.3421 (1)	3.56(6)
C4B	0.1837 (3)	0.2579 (2)	-0.3746 (2)	5.32(8)
C5B	0.1220 (4)	0.2369 (2)	-0.4655 (2)	6.60(9)
C6B	-0.0082 (4)	0.1467 (2)	-0.4702 (2)	5.01(8)
C7B	0.2435 (4)	0.1663 (3)	-0.3216 (3)	7.14(11)
C8B	0.1076 (3)	0.0793 (2)	-0.3274 (2)	5.30(8)
C9B	-0.2427 (3)	0.1835 (2)	-0.3308 (1)	3.93(6)
C10B	-0.3087 (3)	0.2619 (2)	-0.3011 (1)	3.80(6)
C11B	-0.3482 (3)	0.3462 (2)	-0.3545 (1)	3.60(6)
C12B	-0.3322 (3)	0.3591 (2)	-0.4445 (1)	3.64(6)
C13B	-0.2383 (3)	0.4424 (2)	-0.4768 (2)	4.69(8)
C14B	-0.2249 (4)	0.4552 (2)	-0.5608 (2)	5.38(8)
C15B	-0.3065 (4)	0.3884 (2)	-0.6146 (2)	5.21(8)
C16B	-0.4024 (4)	0.3055 (2)	-0.5838 (2)	5.43(9)
C17B	-0.4127 (3)	0.2910 (2)	-0.4992 (2)	4.57(7)

C18B	-0.4032 (3)	0.4193 (2)	-0.3217 (2)	4.45(7)
C19B	-0.4226 (3)	0.4090 (2)	-0.2390 (2)	5.27(8)
C20B	-0.3878 (4)	0.3249 (3)	-0.1876 (2)	5.64(8)
C21B	-0.3320 (3)	0.2508 (2)	-0.2181 (2)	4.94(8)
OW1	0.1783 (2)	-0.0408 (1)	0.0902 (1)	5.62(6)
OW2	0.6305 (3)	0.0082 (2)	0.4156 (1)	9.79(10)

Definition of B(eq.):

$B(eq) = 4/3 \cdot [\, a^2 \cdot B_{11} + b^2 \cdot B_{22} + c^2 \cdot B_{33} + a \cdot b \cdot \cos(\gamma) \cdot B_{12} + a \cdot c \cdot \cos(\beta) \cdot B_{13} + b \cdot c \cdot \cos(\alpha) \cdot B_{23} \,]$

Table V. Torsion Angles (deg) for the two Independent Molecules of (E)-2-(2-phenilbenzylidene)-3-quinuclidinone (VII), labelled A and B; Estimated Standard Deviation in Parentheses.

O1A -C3A -C2A -N1A	179.2(5)	C16A-C17A-C12A-C13A	0.7(5)
C4A -C3A -C2A -N1A	-1.8(3)	C17A-C12A-C11A-C10A	54.3(5)
C4A -C5A -C6A -N1A	1.6(4)	C17A-C12A-C13A-C14A	-1.5(5)
C4A -C7A -C8A -N1A	-2.3(4)	C17A-C16A-C15A-C14A	-0.5(5)
C5A -C4A -C3A -O1A	-120.6(5)	C18A-C11A-C10A-C9A	-176.6(5)
C5A -C4A -C3A -C2A	60.3(4)	C18A-C11A-C12A-C13A	54.0(5)
C5A -C6A -N1A -C2A	58.5(4)	C18A-C11A-C12A-C17A	-127.3(5)
C6A -N1A -C2A -C3A	-59.0(4)	C19A-C18A-C11A-C10A	-0.7(5)
C6A -C5A -C4A -C3A	-59.4(4)	C19A-C18A-C11A-C12A	-179.0(6)
C7A -C4A -C3A -O1A	121.6(4)	C19A-C20A-C21A-C10A	1.3(5)
C7A -C4A -C3A -C2A	-57.4(4)	C20A-C19A-C18A-C11A	-0.4(5)
C7A -C4A -C5A -C6A	57.0(4)	C20A-C21A-C10A-C9A	176.3(6)
C7A -C8A -N1A -C2A	-58.3(4)	C20A-C21A-C10A-C11A	-2.3(5)
C7A -C8A -N1A -C6A	62.4(4)	C21A-C10A-C9A -C2A	-108.7(5)
C8A -N1A -C2A -C3A	61.7(4)	C21A-C10A-C11A-C12A	-179.6(5)
C8A -N1A -C6A -C5A	-62.3(4)	C21A-C10A-C11A-C18A	2.0(4)
C8A -C7A -C4A -C3A	59.0(4)	C21A-C20A-C19A-C18A	0.1(5)
C8A -C7A -C4A -C5A	-56.6(4)	O1B -C3B -C2B -N1B	-177.9(6)
C9A -C2A -N1A -C6A	122.8(5)	C4B -C3B -C2B -N1B	2.2(4)
C9A -C2A -N1A -C8A	-116.6(5)	C4B -C5B -C6B -N1B	4.6(4)
C9A -C2A -C3A -O1A	-2.8(5)	C4B -C7B -C8B -N1B	-0.4(4)
C9A -C2A -C3A -C4A	176.3(6)	C5B -C4B -C3B -O1B	-121.9(5)
C10A-C9A -C2A -N1A	-176.9(5)	C5B -C4B -C3B -C2B	58.0(4)
C10A-C9A -C2A -C3A	5.2(4)	C5B -C6B -N1B -C2B	57.1(4)
C11A-C10A-C9A -C2A	70.0(5)	C6B -N1B -C2B -C3B	-61.8(4)
C12A-C11A-C10A-C9A	1.7(4)	C6B -C5B -C4B -C3B	-61.3(5)
C13A-C12A-C11A-C10A	-124.3(5)	C7B -C4B -C3B -O1B	120.3(5)
C14A-C13A-C12A-C11A	177.2(6)	C7B -C4B -C3B -C2B	-59.8(4)
C15A-C14A-C13A-C12A	1.3(5)	C7B -C4B -C5B -C6B	54.9(5)
C15A-C16A-C17A-C12A	0.3(5)	C7B -C8B -N1B -C2B	-59.2(4)
C16A-C15A-C14A-C13A	-0.3(5)	C7B -C8B -N1B -C6B	61.7(5)
C16A-C17A-C12A-C11A	-178.0(6)	C8B -N1B -C2B -C3B	58.9(4)
8B -N1B -C6B -C5B	-64.5(4)	C8B -C7B -C4B -C3B	58.1(5)
C8B -C7B -C4B -C5B	-57.6(5)	C9B -C2B -N1B -C6B	118.0(5)
C9B -C2B -N1B -C8B	-121.3(5)	C9B -C2B -C3B -O1B	2.4(5)
C9B -C2B -C3B -C4B	-177.5(6)	C10B-C9B -C2B -C3B	3.3(4)
C11B-C10B-C9B -C2B	69.4(5)	C12B-C11B-C10B-C9B	2.6(4)
C13B-C12B-C11B-C10B	-124.8(5)	C14B-C13B-C12B-C11B	-179.1(6)
C15B-C14B-C13B-C12B	1.9(5)	C15B-C16B-C17B-C12B	1.7(5)
C16B-C15B-C14B-C13B	-1.0(5)	C16B-C17B-C12B-C11B	177.4(6)
C16B-C17B-C12B-C13B	-0.8(5)	C17B-C12B-C11B-C10B	57.1(5)

C17B-C12B-C13B-C14B	-0.9(5)	C17B-C16B-C15B-C14B	-0.7(6)
C18B-C11B-C10B-C9B	-177.3(5)	C18B-C11B-C12B-C13B	55.0(5)
C18B-C11B-C12B-C17B	-123.1(5)	C19B-C18B-C11B-C10B	-1.4(5)
C19B-C18B-C11B-C12B	178.7(6)	C19B-C20B-C21B-C10B	0.9(5)
C20B-C19B-C18B-C11B	-0.3(5)	C20B-C21B-C10B-C9B	177.5(7)
C20B-C21B-C10B-C11B	-2.6(5)	C21B-C10B-C9B -C2B	-110.7(5)
C21B-C10B-C11B-C12B	-177.3(6)	C21B-C10B-C11B-C18B	2.9(5)
C21B-C20B-C19B-C18B	0.6(5)		

Chemically both (Z) and (E) molecules are constituted by the 1-azabicyclo[2,2,2]-octan-3-one moiety, substituted at position 2 by a 2-phenylbenzilidene group. The two isomeric molecules are characterized by a double bond between the C2 and C9 carbon atoms, whose substituents can assume the (Z) or the (E) disposition. In fact, the C2-C3 bond is in a *trans* disposition with respect to the C9-C10 bond for the (Z) isomer, while it is in a *cis* disposion in the (E) isomer.

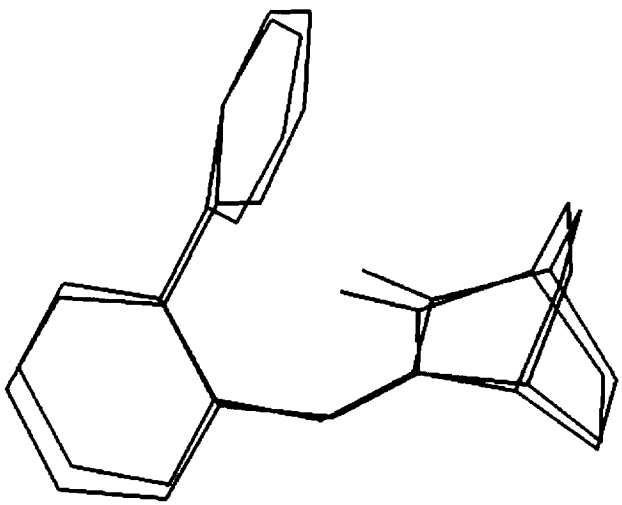


Fig. 4. Overlap of the two indepedent molecules of the monohydrate chloridrate of the (E)-2-(2-phenylbenzylidene)-3-quinuclidinone.

The double bond is nearly planar in the (Z) molecule, as indicated by the value of 0.010 Å of the mean squares deviation of the atoms from the best plane passing through them. For isomer (E) the values of the mean square deviation for the two independent molecules in the asymmetric unit are 0.015 and 0.014 Å, respectively, indicating a greater deviation from the planarity of the atoms of the double bond. This observation is confirmed by the torsion angles around the C2-C9 double bond, which are greater (5.2° and 3.3°) in the (E) isomer compared to that observed for the (Z) isomer (177.3°).

Furthermore, as expected, deviations from the ideal bond angle geometry around the sp^2 carbon atoms of the double bond are observed. For the (Z) isomer, while the C3-C2-C9 angle shows a value of 121.4°, close to the ideal geometry (120°), the C3-C2-N1, N1-C2-C9 and C2-C9-C10 angles, because of the steric hinderance of the substitutions on C2 and C9, assume values of 113.0°, 125.6° and 130.2°, respectively. These large deviations contribute significantly to the release of the intramolecular non-bonded interactions present in this

portion of the molecule. The H10 hydrogen atom, linked to the C9 atom experiences short interactions with the C12, C13, C16 and C17 carbon atoms of the biphenyl moiety with non-bonded distances ranging from 2.6 to 3.5 Å.

The bond angle deviations from an ideal sp^2 geometry observed in both independent molecules of the (E) isomer are of the same magnitude. In particular, while the N1-C2-C9 angle shows almost ideal values (120.1° and 120.3° in the two independent molecules, respectively), being much lower than the value of 128.6° observed in the (Z) isomer, on the contrary, the angle C3-C2-C9 exhibits greater deviations with values of 128.9° and 129° (in the two independent molecules), significantly larger than the corresponding angle in the (Z) isomer (121.4°). Furthermore, the angle C2-C9-C10, that in the *trans* isomer is 130.2° (the grater deviation observed from ideal geometry), in the *cis* isomer exhibits lower deviations with values of 123.7° and 124.5° for the two independent molecules. All these differences contribute substantially to the release of the intramolecular strain occurring between the biphenyl and the 1-azabicyclo[2,2,2]-octan-3-one moieties. Nevertheless, the C=O group [C3=O1] still experiences severe non-bonded intramolecular interactions, which are greater in the *cis* than the *trans* isomer: the average distances between the O1 atom and the C12 and C13 atoms of the biphenyl ring, in both the independent molecules of the *cis* isomer, is 3.3 Å.

The 1-azabicyclo[2,2,2]-octan-3-one portion, in both compounds investigated, shows small bond angle deviations from literature data available for the 1-azabicyclo-2,2,2-octane moiety[16-20]: the differences observed are always the consequence of the substitution on position 2 and 3 of the bicyclic system. In these positions sp^2 atoms substitute sp^3 atoms. As a result the N1, C2, C3, and C4 atoms are now in a planar disposition, with a torsion angle N1-C2-C3-C4 of 2.7° for the *trans* isomer and of -1.8° and 2.2° for the two independent molecules of the *cis* isomer. A partial coniugation between the double bond and the carbonyl moiety is also observed with shortening of the C2-C3 bond lenght, with values of 1.448 Å for the *trans* isomer and 1.474 Å and 1.478 Å for the two independent molecules of the *cis* isomer, smaller than expected for a C-C single bond adjacent to a double bond. In addition, bond angles involving the tertiary C4 and N1 atoms show, on the average, smaller values than tetrahedral, while those involving the secondary C5, C6 and C8 carbon atoms are, on the average, slightly larger. It is worth to note, however, that in the *cis* isomer the differences observed in the angular values involving the N1 atom can be also partially due to protonation.

The diphenyl moiety is found in a non-planar conformation in both structures, with angles between the planes of the phenyl rings of 53.7° in the *trans* isomer and 54.1° and 56.2° in the two molecules of the *cis* isomer. The structural determinations of literature show that the biphenyl moiety takes various values of the dihedral angle, depending on the small energetic barrier to rotation around the central single bond and on enviromental conditions, that is the intra- and the intermolecular interactions exhixting in the crystal[21-23].

The values observd in in our structures are close to the expected mean gas-phase[24] value of 42°, calculated by a static and dynamic model of an unsubstituted biphenyl molecule. The value of the dihedral angle in ortho-substituted biphenyl systems is certainly greater than this value, while meta- and para-susbtitutions seems to have smaller influence[25]. Furthermore, bond angles deformations in the ortho-subsituted diphenyl moieties of both compounds contribute to the release of the intramolecular interactions: in the *trans* isomer the C10-C11-C12 and C11-C12-C13 angles are larger than 120° (122.9° and 123.0°, respectively), while the C18-C11-C12 and C11-C12-C17 are smaller (118.1° and 119.0°, respectively). In the *cis* isomer instead the C10-C11-C12 (121.1° and 121.6° in the two independent molecules) and C11-C12-C17 (121.6° and 121.7°)

angles are larger than 120°, while the C11-C12-C13 (119.9° and 120.4°) and the C12-C11-C18 (120.3° and 119.7°) angles takes pratically ideal values.

Further contributions to the release of the intramolecular interactions comes from the significant rotation occurring around the C9-C10 bond, which further separate atoms of one of the phenyl rings from those of the C2-C9 double bond and its substituents. The angle between the plane of the double bond and that of the phenyl ring directly linked to it is 19.4° in (I). This is more apparent in the *cis* isomer in which the molecule is sterically more hindered. Infact, the C2-C9-C10-C11 and C2-C9-C10-C21 torsion angles are 70.0° and 69.4° or -108.7° and -110.7°, for the two independent molecules, respectively. Also, the plane of the double bond and the plane of the phenyl ring of the diphenyl directly linked to it are 73.9° and 71.6° for the two independent molecules of the *cis* isomer. In this conformation the shortest non-bonded distances between atoms of one phenyl ring and atoms of the 1-aza-[2,2,2]-bicyclo octane group are not smaller than 3.2 Å.

The modes of packing of the (Z)-2-(2-phenylbenzilidene)-3-quinuclidinone and of the (E)-isomer are represented in Figures 5 and 6, respectively. For the (Z)-isomer mainly Van der Waals forces are responsible for the stabilization of the crystal.

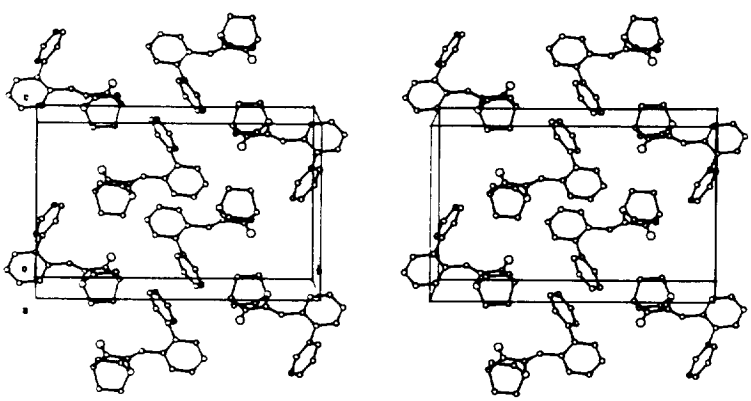


Fig. 5. A stereo view of the mode of packing of the molecules of (Z)-2-(2 phenylbenzylidene)-3-quinuclidinone (VI) projected down the c axis.

In the (E)-isomer crystal, instead, where co-crystallized water molecules and Cl^- ions are present in the unit cell together with N-protonated quinuclidine moiety, electrostatic interactions and hydrogen bonds play a major role in the stabilization of the crystal. In both independent molecules protonated N atoms experience short interactions with Cl^- ions [with $N\text{-}H^+ \cdots Cl^-$ distances of 2.71 and 3.00 Å, for the two independent molecules]. These values fit well with literature data on quinuclidines chloridrates[26].

The observed N-H ··· Cl hydrogen bond distances are the result of a rather strong interaction. In addition, each chlorine ion is hydrogen-bonded to two water molecules with $Cl^- \cdots$ H-O distances of 3.06 and 3.11 Å, for Cl^-A and of 3.13 and 3.17 Å for Cl^-B, respectively. As represented in the Figure 6, layers of quinuclidine moieties alternate with layers of Cl^- and water molecules.

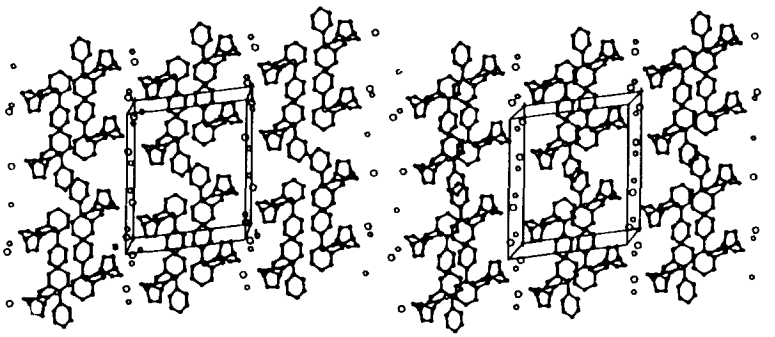


Fig. 6. A stereo view of the mode of packing of the molecules of (E)-2-(2-phenylbenzylidene)-3-quinuclidinone (VII) projected down the a axis.

CONCLUSIONS

The (Z)- and (E)-2-(2-phenylbenzylidene)-3-quinuclidinones have been synthesized and fully characterized by X-ray diffraction analyses. These compounds are to be considered key intermediates in the preparation of 2-benzylidene-3-benzylamino quinuclidines, which have shown to possess a moderate potency on the neurokinin receptors. The structural analyses of the two quinuclidinones have afforded geometric and conformational parameters to be used in molecular modeling studies for the identification of the pharmacophoric requirement of NK-1 antagonists.

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SUPPLEMENTARY MATERIAL

Supplementary material in the form of tables of anisotropic thermal parameters for C, N, O and Cl atoms, positional and isotropic thermal parameters for H atoms, full lists of bond lengths and bond angles with their estimated standard deviations, have been deposited with the Crystallographic Data Centre of Cambridge. Copies may be obtained from the Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom.

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