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CONFIGURATION AND CONFORMATION OF (-)-8-PHENYLMENTHYL 3-AMINO-2-HYDROXY-5-METHYLHEXANOATE

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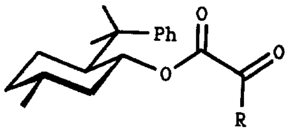
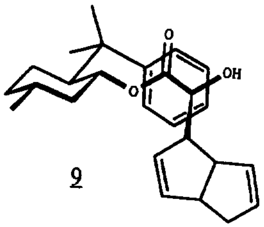
Abstract Conformations of 6aI in solution (NMR, IR) and in the solid state (X-ray) are shown to be similar and it appears, from X-ray data, that the usually invoqued π-π^* *electronic interaction is probably not responsable of the cis conformation. Conformation in solution of the major diastereomer obtained, 3aI, has been shown to be similar to that of 6aI and it is postulate that the asymmetric induction obtained might be due to formation of a bridged species*

Résumé Les conformations de 6aI en solution (RMN, IR) et à l'état solide (rayon-X) sont semblables, de plus il apparait que l'interaction électronique π-π^* *généralement envisagée n'est pas responsable de la conformation cis La conformation du diastéréomère majoritaire 3aI est semblable à celle de 6aI, une espèce pontée est proposée pour expliquer l'induction asymétrique obtenue*

Much attention has been devoted to Corey's 8-phenylmenthol (1) as a powerfull inducer of chirality in Diels-Alder reactions (1,2) and cuprate additions (3) on the corresponding acrylates, or in Grignard additon to (4) and ene reaction of (5) the corresponding α-carbonyl esters 1-1"



1 R=H, 1' R=Me, 1" R=Ph



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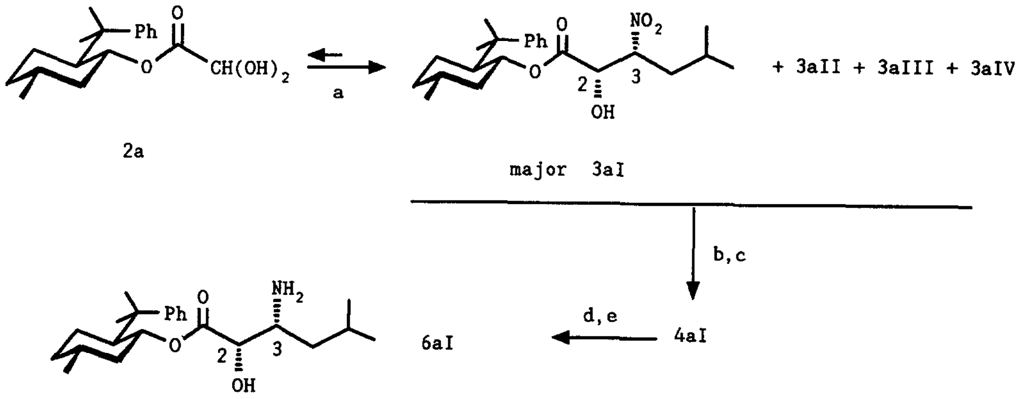
The high levels of asymmetric induction usually obtained upon additions to α-carbonyl esters have been attributed to a through space π π interaction, but only in compound 1 (R=H) has a substantial HOMO-LUMO interaction been detected using fluorescence quantum yield studies (6) This HOMO-LUMO interaction is due to the cis orientation of the carbonyls and to the cis orientation of the phenyl ring with respect to the chain in the transition state (6). Such through-space π . π overlap had already been invoked to explain unusually high asymmetric induction (2,7)

We want to report here our results concerning the structure of the major diastereomer 3aI obtained upon condensation of 1-nitro-3-methylbutane with (-)-8-phenylmenthyl glyoxylate hydrate 2a (8), Scheme 1, and our conclusion about the origin of the observed asymmetric induction.

Scheme 1



a) 1-Nitro-3-methylbutane / KF (12 eq) / THF / 0 °C /72 hrs

b) Et_3Si Triflate / NEt_3 / CH_2Cl_2 / 0 °C / 5-10 mn. c) Purification

d) Ni-Raney / EtOH / 40 atm H_2 / 50 °C / 16 hrs e) MAF / MeOH / rt° (9)

We have shown (8,10) that addition of 1-nitro-3-methylbutane on the α-carbonyl ester hydrate 2a is an equilibrated reaction and that the closer one get to the equilibrium (large amount of KF, long reaction time) the larger is the population in diastereomer 3aI Therefore one can speak in terms of products stability and relate the origin of the asymmetric induction to the origin of the stability of 3aI

Crystal structure of 6aI

Compound 3a was obtained as a mixture (3aI/3aII/3aIII/3aIV = 77/13/10/0) (8,10), purification without epimerization was only possible after protection and lead to pure diastereomer 4I which was then transformed (without epimerization) into compound 6aI

The amino hydroxy ester 6aI being crystalline has been studied by X-ray crystallography

The structure of 6aI, Figure 1, shows that

- the absolute configuration is 2S,3R
- the phenyl ring is in a cis conformation with respect to the chain

A similar cis conformation has already been found in compounds 9 (11), but no detailed analysis of this X-ray structure was given which limits its use to the observation concerning only the cis position of the phenyl ring (12)

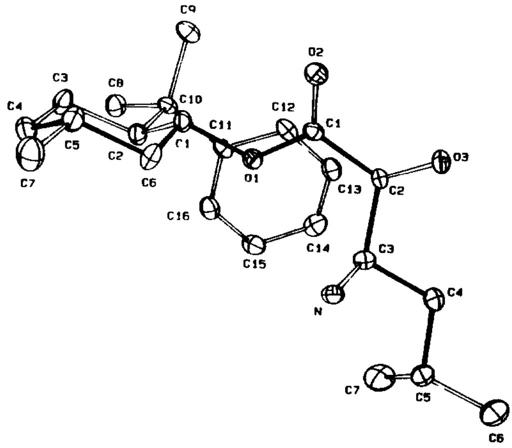


Figure 1 *Ortep plot of one molecule of 6al. Ellipsoids are scaled to enclose 50% of the electronic density and hydrogen atoms are omited.*

A detailed analysis of the X-ray data in our case shows that carbon C1 is 3.5Å distant from carbon C12', Table 1, and situated as drawn on Figure 2 with an offset of 1 36Å and a twist angle of 40° between the π-orbital axis These values indicate that **there is no reasonable overlap between the C1 and C12' π-lobes and, therefore, that there is no significant π.π* interaction.**

However the geometry observed is consistent with the recently proposed model of Hunter and Sanders (13) and suggests that a σ π attractive interaction is present In this model, which explains the basic mechanisms of the known strong attractive interaction between aromatic π-systems, it is shown that the geometries are controlled by electrostatic σ π interactions while the major energetic contribution comes from van der Waals interactions

Therefore, it must be pointed out that the electronic π π* interaction usually invoqued to explain the high levels of asymmetric induction obtained with type 1 compounds (see above) is probably not responsable of the effect, which is not surprizing as charge-tranfer interactions have been shown to be important only in the excited state (13)

Table 1· Some characteristic angles and distances between non-bonded atoms

C1	C11'-C12'-C1 = 90 3° C14'-C12'-C1 = 112 8° C12'-C1 = 3.506 Å
O2	C14'-C12'-C1/C12'-C1-O2 = 17 6° C12'-C1-O2 = 120°

O3-O2 = 2 71 Å O3-O1 = 3.5 Å
N-O3 = 3.07 Å N-O1 = 3 10 Å N-O2 > 3 5 Å

Table 2a Bond Distances in Angstroms

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O1	C1	1.330(4)	C5	C7	1.503(7)	C9′	C10′	1.548(6)
O1	C1′	1.497(4)	C1′	C2′	1.532(5)	C10′	C11′	1.533(5)
C1	O2	1.197(4)	C1′	C6′	1.506(5)	C11′	C12′	1.393(5)
C1	C2	1.542(5)	C2′	C3′	1.583(5)	C11′	C16′	1.398(6)
C2	O3	1.427(4)	C2′	C10′	1.568(5)	C12′	C13′	1.389(6)
C2	C3	1.538(5)	C3′	C4′	1.487(5)	C13′	C14′	1.352(6)
C3	N	1.469(5)	C4′	C5′	1.531(5)	C14′	C15′	1.404(6)
C3	C4	1.543(5)	C5′	C6′	1.524(5)	C15′	C16′	1.357(6)
C4	C5	1.525(6)	C5′	C7′	1.510(6)			
C5	C6	1.526(6)	C8′	C10′	1.562(5)			

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 2b: Bond Angles in Degrees

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C1	O1	C1′	115.8(2)	O1	C1′	C2′	106.3(3)	C2′	C10′	C11′	111.5(3)
O1	C1	O2	124.4(3)	O1	C1′	C6′	106.4(2)	C8′	C10′	C9′	105.6(3)
O1	C1	C2	111.6(3)	C2′	C1′	C6′	113.1(3)	C8′	C10′	C11′	107.0(3)
O2	C1	C2	124.0(3)	C1′	C2′	C3′	105.1(3)	C9′	C10′	C11′	112.6(3)
C1	C2	O3	108.0(3)	C1′	C2′	C10′	114.8(3)	C10′	C11′	C12′	124.2(3)
C1	C2	C3	113.2(3)	C3′	C2′	C10′	112.7(3)	C10′	C11′	C16′	120.2(3)
O3	C2	C3	110.5(3)	C2′	C3′	C4′	112.9(3)	C12′	C11′	C16′	115.6(3)
C2	C3	N	116.0(3)	C3′	C4′	C5′	113.5(3)	C11′	C12′	C13′	122.0(4)
C2	C3	C4	108.8(3)	C4′	C5′	C6′	107.8(3)	C12′	C13′	C14′	120.7(4)
N	C3	C4	109.7(3)	C4′	C5′	C7′	111.6(3)	C13′	C14′	C15′	118.8(4)
C3	C4	C5	114.3(3)	C6′	C5′	C7′	111.8(3)	C14′	C15′	C16′	120.0(4)
C4	C5	C6	109.4(4)	C1′	C6′	C5′	109.9(3)	C11′	C16′	C15′	122.9(4)
C4	C5	C7	113.3(4)	C2′	C10′	C8′	109.5(3)				
C6	C5	C7	112.1(4)	C2′	C10′	C9′	110.2(3)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

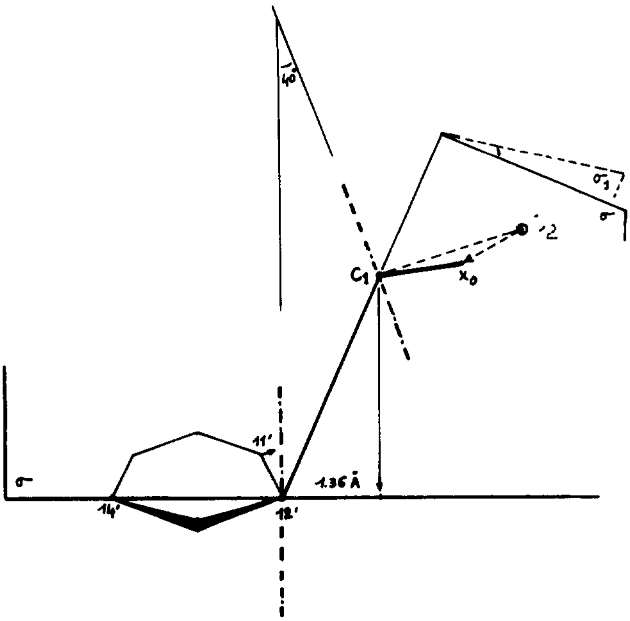


Figure 2. x_O = *orthogonal projection of* O2 *(situated in* σ_1 *plane) on* σ*-plane*
C12'-C1-x_O = 121.2° *and* C1-x_O = 1.05Å *are calculated using the data of* Table 1

Table 3 Some dihedral angles

C3'-C2'-C10'-C11' = -163.7(4)°
C2'-C10'-C11'-C12' = -112.3(5)°
C2'-C1'-O1-C1 = +151.0(4)°
C1'-O1-C1-C2 = +174.4(3)°
O2-C1-C2-O3 = +21.5(6)°

C1-C2-C3-N = -52.3(5)°
C1-C2-C3-C4 = -176.4(4)°
O3-C2-C3-N = +69.0(5)°
C2-C3-C4-C5 = -168.1(4)°

Another important feature of this structure is the folding of the chain probably due to a strong O2-HO3 H-bond (O2-O3 = 2.71Å) which brings H2 and H3 above the phenyl ring and more or less in the shielding cone of the ring.

All bond distances and bond angles found are in the normal range as shown on Table 2. Important dihedral angles are given on Table 3.

^{1}H NMR of 6aI and 3aI (solution)

Some ^{1}H RMN data of compounds **6aI**, and **3aI** in solution ($CDCl_3$) are given on table 4

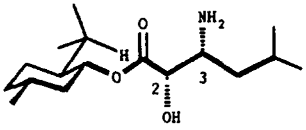
Table 4: Chemical shifts and coupling constants of H2 and H3

	H2 (ppm)	$J_{2,3}$ (Hz)	H3 (ppm)	$J_{3,4}$ (Hz)
6aI	2.98 (-1 14)^a	2 2	2 65 (-0 5)^a	7 and 2 2
3aI	3 05 (-1 3)^b	3 5	4 22 (-0 63)^b	8 5 and 5 5

a) δ(Hn) in **6aI** - δ(Hn) in **6bI**. b) δ(Hn) in **3aI** - δ(Hn) in **3bI**

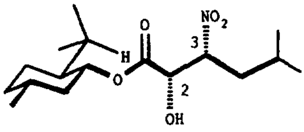
Compound 6aI

It apprears that in compound **6aI** protons H2 and H3 are respectively shielded by 1 14 and 0 5ppm compared to the same protons in the menthyl derivative **6bI** which is consistent with a cis relationship between the phenyl ring and the OCO-CH(OH)-CH(NH_2)-iBu chain



6bI

δ(H2) = 4 12 ppm
δ(H3) = 3.15 ppm



3bI

δ(H2) = 4.35 ppm
δ(H3) = 4 85 ppm

It is noteworthy that the value of the dihedral angle, θ=55°± 2° (14), determined from the 2 2Hz H2-H3 coupling constant and the Karplus-Conroy curve, is similar to the dihedral angle found in the solid state, θ=52° (Table 3) *This angle is comptatible but with a weak H-bond between NH_2 and OH*
On the other hand, because of an OH-O=C H-bond, which can also be postulated to be present in solution (on the basis of IR data γ_{OH} =3400cm-1, slightly broadened), the dihedral angle O2-C1-C2-O3 should not change much from the solid state to the solution
Therefore we can conclude that there would be but minor changes in the conformation of the O-CO-CH(OH)-CH(NH_2)-iBu chain from the solid state to the solution

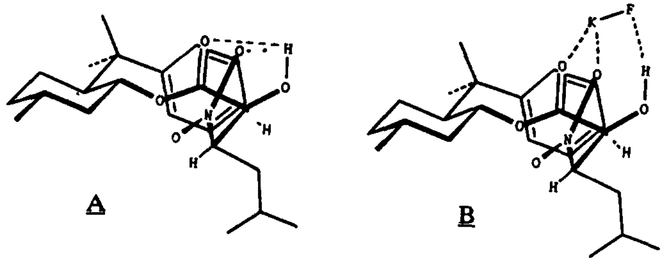


Figure 4

Compound ***3aI***

As compound **3aI** has been transformed into compound **6aI** in three steps without possible epimerisation, configuration of compound **3aI** is also (2S,3R)

One notices that in compound **3aI** protons H2 and H3 are also shielded by 1.3 and 0.63ppm respectively compared to the same protons in the menthyl derivative **3bI** which indicates that, as in compound **6aI**, the phenyl ring must be in a cis position with respect to the chain.

On the other end, the H2-H3 coupling constant, 3.5Hz, leads (from the Karplus-Conroy curve) to an average O3-C2-C3-N dihedral angle of about 49° ± 2° similar (14) to that found in compound **6aI** (52° ± 2°)

Therefore, taking also into account a OH-O=C H-bond already invoked for ***6aI****, one can conclude that, in solution, conformation* ***A*** *of (2S,3R)-****3aI*** *is similar to the conformation of (2S,3R)-****6aI***

On examination of molecular models one can notice that a "bifurcate" (15) asymmetric three-centre hydrogen bonding might be possible (**A**, Figure 4) which would probably participates to the stability of the conformation

Conclusion

From comparison of X-ray structure with NMR data (and some IR data) it can be postulated that there are but minor changes in the conformation of compound **6aI** from the solid state to the solution

It comes out also that the conformation (**A**) of the major and more stable isomer obtained, (2S,3R)**3aI**, is similar to that of (2S,3R)**6aI** and is caracterized by

- a cis position of the phenyl ring with respect to the chain,
- a dihedral angle O3-C2-C3-N of about 50° ($J_{2,3}$=3.5Hz),
- a dihedral angle O2-C1-C2-O3 close to 20° (OH-O=C H-bond)

These results reinforce the hypothesis (8) that KF, when used in large excess and in aprotic solvent can easily form, from conformation **A**, the bridged species **B** (16), Figure 4, causing an extra stabilisation of the already-more-stable conformer **A** and an increase of the asymmetric induction

We can therefore postulate that the asymmetric induction obtained in this nitro aldol addition is very probably due to the formation of the bridged species ***B***

Table 5· Positional Parameters and their E S D

Atom	x	y	z	B(Å^2)
O1	0 8261(2)	0 1135(1)	0 9268(6)	2 72(7)
C1	0 8208(3)	0 0801(2)	1 0867(8)	2 37(9)
O2	0 7577(3)	0 0785(1)	1 2298(6)	3 62(7)
C2	0 9078(4)	0 0444(2)	1 0691(8)	2 7(1)
O3	0 8799(2)	0 0020(1)	1 1868(6)	3 04(7)
C3	0 9371(4)	0 0328(2)	0 8231(9)	3 1(1)
N	0 8557(3)	0 0174(1)	0 6738(7)	2 77(8)
C4	1 0198(4)	-0 0055(2)	0 826(1)	3 7(1)
C5	1 0708(4)	-0 0131(2)	0 598(1)	4 1(1)
C6	1 1345(5)	-0 0581(2)	0 608(1)	5.6(2)
C7	1 1295(5)	0 0295(3)	0 519(1)	6 1(2)
C1'	0 7398(3)	0 1472(2)	0 9150(9)	2 6(1)
C2'	0 7810(4)	0 1943(2)	0 822(1)	2.9(1)
C3'	0 6868(4)	0 2275(2)	0 790(1)	3 8(1)
C4'	0 6078(4)	0 2049(2)	0 649(1)	3 6(1)
C5'	0 5730(4)	0 1566(2)	0 740(1)	3 4(1)
C6'	0 6641(3)	0 1244(2)	0 761(1)	3 4(1)
C7'	0 4939(4)	0 1347(2)	0 591(1)	4 8(1)
C8'	0 8797(4)	0 2708(2)	0 895(1)	3 9(1)
C9'	0 8288(4)	0 2209(2)	1 2221(9)	4 0(1)
C10'	0 8637(4)	0 2180(2)	0 9724(9)	2 6(1)
C11'	0 9639(4)	0 1924(2)	0 9466(9)	2 9(1)
C12'	1 0097(4)	0 1662(2)	1 118(1)	3 6(1)
C13'	1 1011(4)	0 1440(2)	1 087(1)	3 7(1)
C14'	1 1497(4)	0 1473(2)	0 886(1)	4 2(1)
C15'	1 1058(4)	0 1736(2)	0 710(1)	3 9(1)
C16'	1 0163(4)	0 1950(2)	0 742(1)	3 9(1)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as (4/3) [a^2ß(1,1)+b^2ß(2,2)+c^2ß(3,3)+ab(cos *gamma*)ß(1,2) +ac(cos beta)ß(1,3)+bc(cos alpha)ß(2,3)]

It must also be pointed out that the usually invoqued $\pi \pi^*$ electronic interaction (2,6,7) is probably not responsable of the cis conformation nor of the high levels of asymmetric induction obtained in type **1** compounds However to explain the behavior of such compounds, one can envisage Hunter and Sanders' model which is based on a classical aromatic $\pi.\pi$ attraction mainly due to σ-π electrostatic interaction and van der Waals interaction

Experimental section

Suitable single crystal of **6aI** were obtained by slow evaporation of solutions at room temperature A systematic search in reciprocal space using a Philips PW1100/16 automatic diffractometer showed that crystals of **6aI** belong to the orthorhombic system

The unit-cell dimensions and their standard deviations were obtained and refined at -100°C with CuKα radiation (λ =1 5418 Å) by using 25 carefully selected reflections and the standard Philips software Final results $C_{23}H_{32}NO_3$, mol wt =370 52, a=13 428(4), b=28 023(6), c=5 900(2) Å, V=2220 Å^3, Z=4, d_{calc}=1.108gcm^{-1},μ=5.408 cm^{-1}, F_{000}=804, space group=$P2_12_12_1$

A single crystal of O 28 *0 24 *0 20 mm^3 was cut out from a cluster of crystals and glued at the end of a glass wire mounted on a rotation-free goniometer head All quantitative data were obtained at -100°C achieved with a local-built gas flow device on the same diffractometer using graphite monochromated radiation The vertical and horizontal apertures in front of the scintillation counter were adjusted so as to minimize the background counts without loss of net peak intensity at the 2σ level The total scan width in the $\theta/2\theta$ flying step-scan mode used was Δw=0 9 + 0 143tg(θ) with a step-width of 0 05 deg and a scan speed of 0 024 degs^{-1} 1501 +h+k+l reflections were recorded (3°<θ<52°) The resulting data-set was transfered to a VAX computer and for all subsequent calculations the Enraf-Nonius SDP/VAX package (17) was used with the exception of a local data reduction program

Three standard reflections measured every hour during the entire data collection period showed no significant trend

The raw step-scan data were converted to intensities using the Lehmann-Larson (18) method and then corrected for Lorentz and polarisation factors A unique data set of 1384 reflections having I>3σ(I) was used to determine and refine the structure

The structure was solved using MULTAN (19) After refinement of the heavy atoms, a difference-Fourier map revealed maximas of residuals electronic density close to the positions expected for hydrogen atoms, they were introduced in structure factor calculations by their computed coordinates (C-H=0 95Å) and isotopic temperature factors such as B(H)=1 3Beqv(C)Å^2 but not refined The NH_2 and OH hydrogen atoms were not introduced The absolute configuration was determined by comparing xyz and -x-y-z refinements Full least-squares refinement converged to R(F)=0 065 and Rw(F)=0 097 ($\sigma^2(F^2)= \sigma^2_{counts} + (pI)^2$) The unit-weight observation was 1 88 for p=0 08 A final difference map revealed no significant maxima The scattering factor coefficients and anomalous dispertion coefficients come from ref 20

Table 5 lists the atomic coordinates of all non-hydrogen atoms

All protons NMR spectra were recorded on 200 MHz Bruker, WP 200 SY and AC 200, in $CDCl_3$ and refered to TMS

Supplementary material Table SI Positional Parameters and their E S D, Table SII Temperature factors for anisotropic atoms, Table SIII Hydrogen atoms positional parameters, Table SIV Observed and calculated structure factors amplitudes (*10) for all observed reflections (11 pages)

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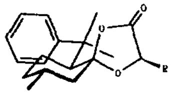

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20) Cromer D T, Waber J T · *International Tables for X-ray Crystallography*, The Kynoch Press Birmingham, Vol IV, **1974**, (a) Table 2 2b, (b) Table 2 3 1