SYNTHESIS AND PHYSICO-CHEMICAL PROPERTIES OF (R,S)-6-DITRIDEUTERIOMETHYLAMINO-4,4-DIPHENYLHEPTAN-3-ONE HYDROCHLORIDE (METHADONE-d_6)

Bruno M.Gérardy [a], Jacques H.Poupaert [a*], Daniel Vandervorst [a], Pierre Dumont [a], Jean-Pierre Declerq [b], Maurice Van Meerssche [b], and Philip S.Portoghese [c]

[a] Department of Medicinal Chemistry, School of Pharmacy, UCL, 73 Avenue E. Mounier, B-1200 Brussels, Belgium

[b] Laboratoire de Chimie Physique et de Cristallographie, UCL, Bâtiment Lavoisier, 1 Place L. Pasteur, B-1348 Louvain-la-Neuve, Belgium

[c] Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, 308 Harvard Street S.E., Minneapolis, Minnesota 55455, USA

SUMMARY

A reaction sequence is described to synthesize (R,S)-6-ditrideuteriomethylamino-4,4-diphenylheptan-3-one hydrochloride (methadone-d_6.HCl) in 10.5% overall yield starting from dimethylamine-d_6 hydrochloride. While methadone-d_6.HCl had rather similar physico-chemical properties compared to methadone.HCl in the solid phase, a divergent behaviour was observed in solution (pKa, chromatographic and ^{13}C-NMR data). A higher basicity along with a more important hydrophilicity were observed for the d_6-derivative. A ^{13}C-NMR study showed significant differences in the ^{13}C chemical shifts, which were attributed in part to the intrinsic nature of D itself and in part to a conformational perturbation. The longer duration of antinociceptive action, along with higher $t_{1/2}$ and clearance, and the depression of the metabolic N-demethylation process were the only biological properties modified by the deuteration.

Key words : methadone, deuterium, isotopic effects, ^{13}C-NMR, X-ray, antinociceptive activity

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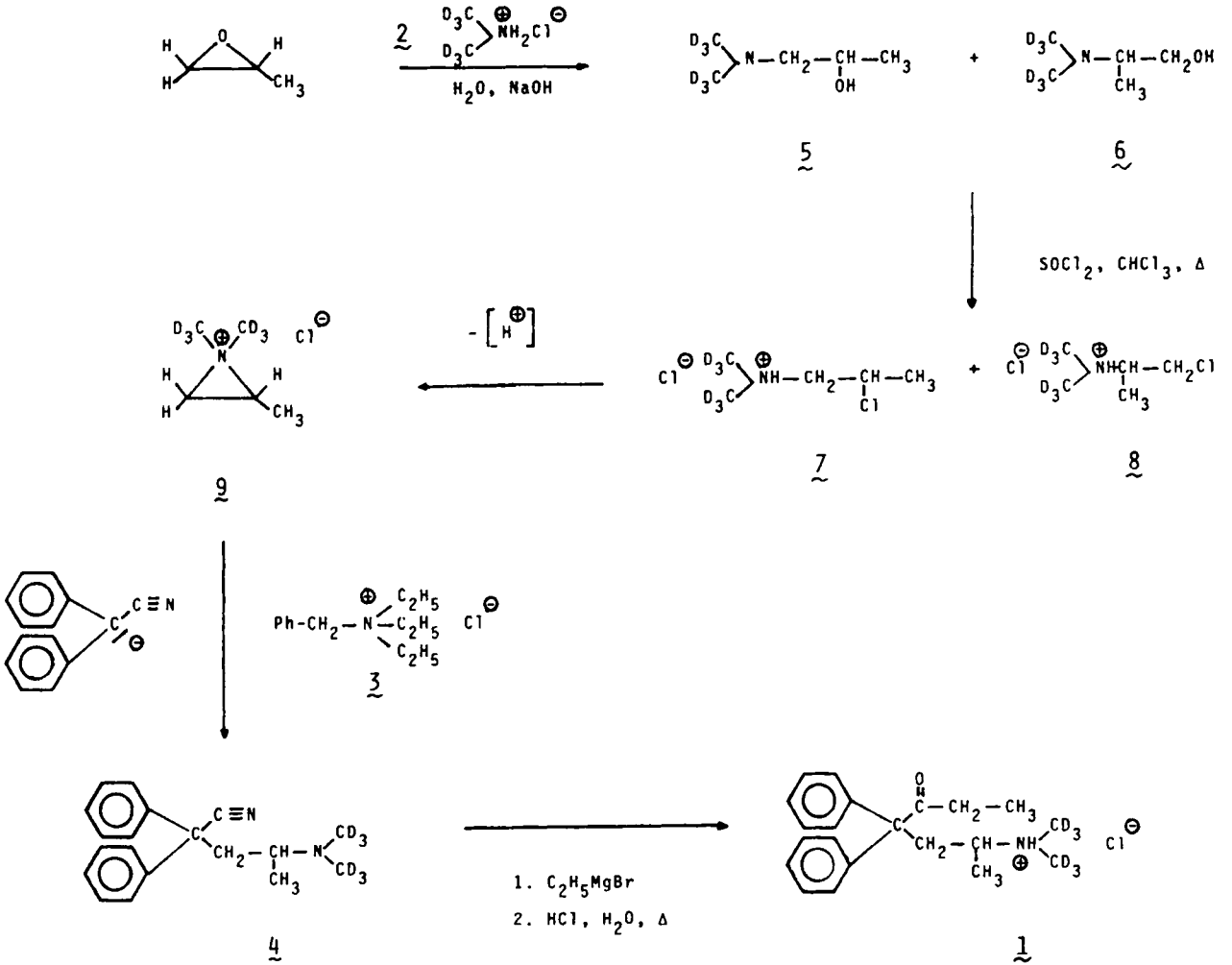


Scheme 1

I. SYNTHETIC APPROACH

In a effort to investigate the impact of introducing deuterium in drugs on their pharmacologic properties and pharmacokinetic profile (1), we have synthesized (R,S)-6-ditrideuteriomethylamino-4,4-diphenylheptan-3-one hydrochloride (methadone-d_6.HCl, 1). As the major metabolic pathway of methadone derives from a N-demethylation process, which is governed by a primary isotopic effect, it was anticipated that the molecular modification presented here could possibly induce a metabolic switching (2). Consequently, important modifications in the duration of pharmacological action could be expected. Moreover, the expected modifications of hydrophilicity and basicity were also susceptible of producing pharmacokinetics deviations compared to methadone.

The reaction sequence shown in the scheme 1 was adapted from the well-know BOCKMUHL synthesis of methadone (3). Initially, various alternative methods were investigated to introduce the ditrideuteriomethylamino moiety in a later stage of the synthesis, including the methods of HENKEL (4) and EASTON (5). These approaches proved either unsuccessful or of poor yield. Therefore, the target compound was finally obtained through a carefully optimized sequence of classical reactions starting from the commercially-available ditrideuteriomethylamine hydrochloride 2. The key-alkylation step was carried out using a phase-transfer catalyst (benzyltriethylammonium chloride, 3) as reported previously (6) to give recrystallized (R,S)-4-ditrideuteriomethylamino-4,4-diphenylpentanenitrile 4 in 32.5% yield. This compound was converted to 1 according to BOCKMUHL and EHRHARDT (3) in 72% yield (deuterium content : 98%). The overall sequence had 10.5% yield based on ditrideuteriomethylamine hydrochloride 2.

It should be noted that no efforts were devoted to purifying the isomeric aminoalcohols 5 and 6 and the subsequent ß-chloroamines 7 and 8, since both series of compounds led to the same aziridinium intermediate 9 (7).

II. PHYSICO-CHEMICAL PROPERTIES

II.1. Behaviour in the solid phase. X-ray diffraction studies.

While (R,S)-methadone hydrochloride 10 had in our hands a melting point (mp) of 235°C [litt (8), mp 235°C], 1 had initially a mp of 227-230°C; repeated recrystallizations from isopropanol:ether mixtures (90:10 v/v) raised the melting point up to 233°C. Differential thermal analysis demonstrated that 1 was a pure product. Comparative inspection of the IR spectra of 1 and 10 (dispersed in KBr) revealed that these compounds most probably had rather similar solid features, and in this respect the $\geq C=O$ (table 1) was fairly diagnostic : the fact that the ν C=O was not affected in its position was consistent with the existence of so-called extended conformers with no interaction between the $\geq \overset{+}{N}-H$ and $\geq C=O$ moieties. This hypothesis was confirmed subsequently by X-ray diffraction studies carried out on 1 and 10. On the other hand, it was observed that signals arising either from C-D as well as N-H vibrators were deeply affected in their forms and intensities and showed the expected shifts to lower wave numbers.

X-RAY DIFFRACTION DATA

The crystals were monoclinic with the same space groupe *Cc* . The intensities were collected on a Syntex P2 diffractometer using

Table 1. PHYSICO-CHEMICAL PARAMETERS OF (R,S)-6-METHADONE HYDROCHLORIDE AND (R,S)-6-METHADONE-d_6 HYDROCHLORIDE.

PARAMETERS	METHADONE.HCl	METHADONE-d_6.HCl
mp (°C)	235	233
IR (ν C=O, cm^{-1}) [a]	1705	1705
pKa [b]	8.62	8.71
Rf (TLC) [c]	0.79	0.58
Rf (HPTLC) [d]	0.84	0.63
k' (HPLC) [e]	5.67	6.94
GLC (Rt, min) [f]	9.06	9.06

[a] Perkin-Elmer 580 Infrared Spectrophotometer ; reference : polystyrene ; resolution : 2.8 cm^{-1} ; 0.5 % in KBr .

[b] Multi Dosimat E415 Metrohm-Herisau ; a 0.02 M solution of 1 or 10 is titrated by a 0.01 N aqueous solution of NaOH (23°C) .

[c] Silica gel 60F-254, Merck ; benzene:methanol:33% ammonia (85:15:0.65, v/v) .

[d] Silica gel 60F-254, Merck ; benzene:methanol:33% ammonia (85:15:0.65, v/v) .

[e] Solvent delivery system : Waters 6000A, flow rate : 2.5 ml/min ; column : Radial-Pak, C-8 10 µ, length 10 cm, int. diam. 0.8 cm ; UV detector : Pye Unicam Model LC3, operated at 235 nm ; solvent : methanol:2N ammonium hydroxyde: 5N aqueous acetic acid (270:20:10, v/v) .

[f] Hewlett-Packard 5710A equipped with N-P detector and Perkin-Elmer Data-System Sigma 10; column : OV17 3%, length 6 ft, int. diam. 2 mm ; carrier gas : He, 24 ml/min ; temperature program : initial-200°C (12 min), final-240°C, rate 20°C/min .

graphite monochromatized MoK_α radiation (λ = 0.7107 Å) up to 2Θ = 47°. The crystal data are summarized in table 2.

Densities of 1 and 10 are nearly the same, the difference between the molecular weights (about 2%) being compensated by a similar

difference between the volumes of the unit cells. In both cases, there are two molecules (A and B) in the asymmetric unit. The coordinates of the chlorine atoms were derived from the interpretation of a Patterson map and the other non hydrogen atoms were obtained by the application of the DIRDIF 81 program (9). The refinement was carried out by the SHELX 76 program (10) with anisotropic thermal parameters for the non hydrogen atoms. The phenyl rings were considered as rigid groups with bond lenghts fixed at 1.395 Å and angles at 120°. The hydrogen atoms were located in computed positions.

As could be supposed from the unit cell parameters, the two structures are perfectly isomorphous which confirms the chemical identity of 1 and 10. The refinement of 10 gave much more accurate results and a better reliability index than for 1. This is probably due to a partial disorder of this last compound, caused perhaps by not fully complete deuteriation. For this reason, the following description will be given for 10 only. The final atomic

Table 2. Crystal data of 1.HCl and 10.HCl

	1	10
a	16.324(6)Å	16.265(5)Å
b	9.823(5)	9.759(5)
c	26.476(11)	26.370(11)
β	109.40(3)°	110.22(3)°
V	4004(3)Å^3	3928(3)Å^3
M	351.9	345.9
Z	8	8
D_x	1.17 g.cm^{-3}	1.17 g.cm^{-3}
Number of reflections		
. collected	2968	2908
. observed($I > 2.5\sigma_I$)	2120	1989
R index	0.127	0.049

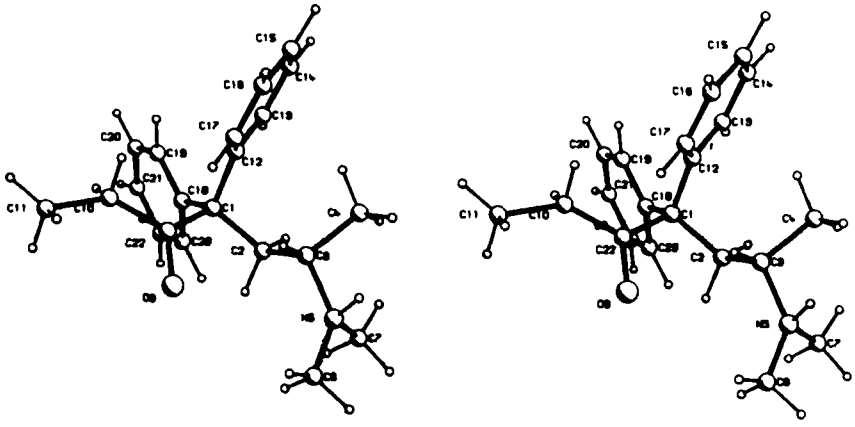


Fig.1. Stereoscopic view of molecule 10 and numbering of the atoms

coordinates are given in table 3 following the numbering scheme of figure 1. Tables 4 and 5 list bond lengths and valence angles. There is a good agreement between the two independent molecules except for the C(10)-C(11) distance which is much shorter in molecule A, because of the high thermal parameter of C(11) in this molecule. Hydrogen bonds link the chlorine ions to the nitrogen atoms of the molecules (d N(5)....Cl = 3.02 and 3.03 Å, d H(5)....Cl = 1.95 and 2.00 Å). The packing of the molecules and the chlorine ions is shown in figure 2. The conformations are very similar to that published for (S)-methadone hydrobromide (11). Some torsion angles are compared in table 6.

II.2. Behaviour in solution.

The base strengthening effect of deuterium observed for 1 (Δ pKa 0.09 ± 0.01) is of the same order as that found in the literature for morphine-NCD_3 (Δ pKa 0.12), codeine-NCD_3 (Δ pKa 0.13) and 2-phenylethylamine-1-d_2 (Δ pKa 0.10) (12). So, as 1 appears to be a stronger base than 10, we could expect that 1 would interact

Table 3. Atomic coordinates of 10 (x 10^4) and B_{eq} values ($Å^2$).

	Molecule A				Molecule B			
	x	y	z	B_{eq}	x	y	z	B_{eq}
Cl	0	3340 (2)	0	5.47	2776 (2)	6 (2)	7357 (1)	4.79
C1	-241(5)	-1652(7)	1508(3)	3.49	6291(4)	2050(7)	9342(3)	3.09
C2	452(5)	-777(7)	1360(3)	3.44	5337(4)	1481(7)	9200(3)	3.38
C3	75(5)	282(7)	901(3)	3.58	4795(5)	1403(7)	8584(3)	3.69
C4	-44(5)	-331(8)	337(3)	4.93	4251(5)	2676(8)	8345(3)	4.85
N5	684(4)	1499(7)	978(3)	4.65	4147(4)	205(6)	8475(2)	4.23
C6	687(8)	2380(9)	1442(4)	7.71	4584(6)	-1165(8)	8502(4)	5.35
C7	1595(5)	1158(11)	1004(4)	6.25	3560(6)	218(11)	8793(3)	5.74
C8	-669(6)	-789(9)	1835(3)	4.24	6872(5)	989(9)	9182(3)	3.78
O9	-470(5)	400(7)	1927(3)	6.21	6561(4)	-98(6)	8983(2)	5.39
C10	-1288(7)	-1477(10)	2073(4)	6.85	7831(5)	1271(9)	9313(3)	4.80
C11	-1738(8)	-616(13)	2329(5)	9.43	8243(6)	464(12)	8970(4)	7.70
C12	-946(3)	-2177(5)	982(2)	3.42	6720(3)	2213(5)	9965(2)	3.31
C13	-743(3)	-3274(5)	708(2)	4.04	6445(3)	1407(5)	10313(2)	3.83
C14	-1323(3)	-3658(5)	201(2)	5.75	6859(3)	1524(5)	10871(2)	4.69
C15	-2107(3)	-2943(5)	-32(2)	5.91	7548(3)	2447(5)	11081(2)	5.71
C16	-2310(3)	-1845(5)	243(2)	5.50	7824(3)	3253(5)	10733(2)	5.87
C17	-1729(3)	-1462(5)	750(2)	4.45	7410(3)	3136(5)	10175(2)	4.92
C18	223(3)	-2858(6)	1881(2)	3.60	6254(3)	3410(5)	9039(2)	3.47
C19	-242(3)	-4049(6)	1897(2)	4.64	6412(3)	3452(5)	8552(2)	3.96
C20	171(3)	-5121(6)	2240(2)	5.75	6297(3)	4673(5)	8261(2)	5.18
C21	1049(3)	-5003(6)	2567(2)	6.08	6023(3)	5852(5)	8456(2)	5.96
C22	1514(3)	-3813(6)	2551(2)	6.09	5865(3)	5310(5)	8943(2)	5.34
C23	1101(3)	-2740(6)	2208(2)	4.29	5980(3)	4589(5)	9235(2)	4.41
H2	880	-1452	1242	8.22	5389	460	9366	8.22
H2'	829	-212	1717	8.22	4990	2131	9389	8.22
H3	-561	584	906	8.22	5269	1267	8336	8.22
H4	-486	-1194	257	8.22	4690	3541	8413	8.22
H4'	591	-670	343	8.22	3782	2851	8545	8.22
H4"	-299	428	23	8.22	3910	2552	7916	8.22
H5	430	2094	611	8.22	3718	380	8064	8.22
H6	20	2612	1405	8.22	5008	-1136	8265	8.22
H6'	1036	3322	1443	8.22	4091	-1946	8345	8.22
H6"	1003	1831	1814	8.22	4967	-1398	8918	8.22
H7	1562	535	659	8.22	3257	1214	8765	8.22
H7'	1922	595	1371	8.22	3934	-3	9211	8.22
H7"	1955	2086	1000	8.22	3058	-552	8638	8.22
H10	-924	-2224	2367	8.22	7911	2345	9242	8.22
H10'	-1770	-1994	1740	8.22	8172	1036	9734	8.22
H11	-2172	-1225	2469	8.22	8928	728	9087	8.22
H11'	-2115	132	2041	8.22	7919	693	8547	8.22
H11"	-1269	-98	2668	8.22	8180	-616	9038	8.22
H13	-130	-3813	886	8.22	5910	696	10147	8.22
H14	-1164	-4522	-8	8.22	6639	883	11138	8.22
H15	-2568	-3289	-417	8.22	7885	2512	11516	8.22
H16	-2938	-1346	68	8.22	8362	3953	10907	8.22
H17	-1904	-636	962	8.22	7633	3766	9916	8.22
H19	-920	-4146	1640	8.22	6632	2549	8400	8.22
H20	-189	-6042	2253	8.22	6422	4728	7890	8.22
H21	1364	-5820	2842	8.22	5916	6797	8240	8.22
H22	2186	-3701	2818	8.22	5621	6687	9099	8.22
H23	1455	-1805	2205	8.22	5832	4508	9608	8.22

Table 4. Interatomic Distances (Å)

	molecule A	*molecule B*
C2 --- C1	1.567 (9)	1.566 (9)
C8 --- C1	1.534 (10)	1.557 (10)
C12 --- C1	1.550 (8)	1.555 (7)
C18 --- C1	1.552 (8)	1.539 (8)
C3 --- C2	1.548 (9)	1.559 (8)
C4 --- C3	1.552 (9)	1.528 (9)
N5 --- C3	1.515 (9)	1.534 (9)
C6 --- N5	1.494 (10)	1.505 (9)
C7 --- N5	1.495 (10)	1.473 (9)
O9 --- C8	1.207 (9)	1.214 (8)
C10 --- C8	1.514 (11)	1.501 (10)
C11 --- C10	1.428 (12)	1.518 (11)

Table 5. Bond Angles (°)

	molecule A	*molecule B*
C8 -C1 -C2	110.3 (6)	110.1 (6)
C12 -C1 -C2	109.3 (5)	109.6 (5)
C12 -C1 -C8	110.2 (5)	105.2 (5)
C18 -C1 -C2	109.7 (5)	108.9 (5)
C18 -C1 -C8	106.0 (5)	110.6 (5)
C18 -C1 -C12	111.3 (5)	112.5 (5)
C3 -C2 -C1	115.7 (5)	115.1 (5)
C4 -C3 -C2	112.1 (6)	115.4 (6)
N5 -C3 -C2	110.7 (5)	109.7 (5)
N5 -C3 -C4	106.8 (6)	106.3 (5)
C6 -N5 -C3	112.2 (6)	112.7 (6)
C7 -N5 -C3	115.1 (6)	115.2 (6)
C7 -N5 -C6	111.6 (7)	111.7 (6)
O9 -C8 -C1	119.8 (7)	119.8 (6)
C10 -C8 -C1	119.0 (7)	119.7 (7)
C10 -C8 -O9	121.0 (8)	120.4 (7)
C11 -C10 -C8	117.2 (8)	113.9 (7)
C13 -C12 -C1	118.9 (3)	120.6 (3)
C17 -C12 -C1	120.6 (3)	119.4 (3)
C19 -C18 -C1	120.1 (3)	121.1 (3)
C23 -C18 -C1	119.9 (3)	118.7 (3)

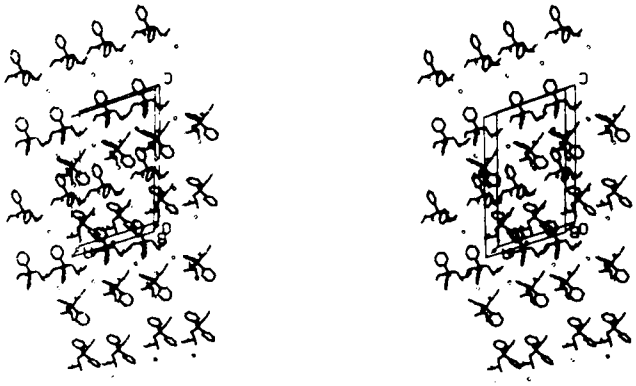


Fig.2. Packing of the molecules in the crystal

more strongly with the weakly acidic Si-OH groups (pKa 6-8) of silicagel (13). The observed results in TLC and HPTLC confirmed this hypothesis (**table 1**). 1, as the protonated form, was also more retained on a reverse-phase HPLC-column. This means that in a rather lipophilic medium, 1 is more soluble in the C-8 stationnary phase than 10 and this can be the case if 1 undergoes a conformation change to a conformer in which the polar groups (ammonium and ketone moieties) are masked by a hydrophobic shield offered by the phenyls and the carbon backbone. This situation is encountered in a conformer (termed as pseudo-cyclic) already described in the literature, principally on the basis of ^{1}H-NMR data (14,15)

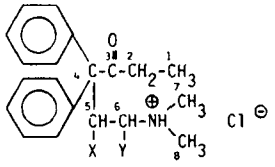
Table 6. Torsion angles in the two independant molecules of (R,S)-methadone hydrochloride and in (S)-methadone hydrobromide

	This work		
	Molecule A	Molecule B	(S)-methadone.HBr [10]
C1-C8-C10-C11	- 174	- 153	- 157
C2-C1-C8-O9	2	0	- 12
C8-C1-C2-C3	- 76	- 71	- 76
C1-C2-C3-N5	151	149	146
C2-C3-N5-C6	- 71	- 75	- 75

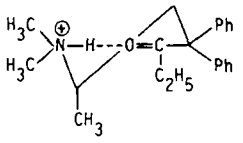
and theoretical calculations (16,17). In order to test this point, we have undertaken a ^{13}C-NMR study of 1, 10 and related congeners [(R,S)-isomethadone.HCl 11, (R,S)-erythro-5-methyl-methadone.HCl 12, (R,S)-threo-5-methyl-methadone.HCl 13 and normethadone.HCl 14] (table 7). While deuterium isotope effects on ^{13}C-NMR chemical shifts are extremely useful for spectrum assignments (18), it should be kept in mind that the importance as well as the direction of the spectral modifications induced by the deuterium remain at the present time somewhat unpredictable (19). So far, most deuterium isotope effects on ^{13}C shifts are shielding (20); deshielding effects have been reported in those rare cases where perturbations were induced by the presence of deuterium on conformational equilibria (21) or on the ability to form hydrogen bonds (22,23).

The ^{13}C-NMR spectrum of 10 in deuteriochloroform is concentration-dependent. We have observed that at high concentrations (0.5-1.0 M solutions), two signals of different areas are observed at 40.0 and 37.3 ppm for the dimethylamino carbons 7 and 8; upon dilution to 0.125 M, a single signal remain at 38.9 ppm. Further dilution down to 0.050 M does not modify the spectrum anymore. Therefore, the spectrum of 1 was recorded at 0.125 M. Modifications in the chemical shifts were observed for carbons 3, 5 and 6 and were of deshielding nature. In spite of the fact that these differences were small, they were far beyond the experimental errors of the instrument. In view of the evidences obtained by chromatography and pKa measurements, the existence of a substantially higher proportion of 1 (compared to 10) in a pseudocyclic internally hydrogen bonded state (table 7, formula b) was already anticipated. To test wether the magnitude and the direc-

Table 7. $\{^1H\}^{13}C$-NMR chemical shifts (δ, ppm) of methadone hydrochloride and its congeners in $CDCl_3$



(a)



(b)

COMPOUNDS	X	Y	1	2	3	4	5	6	7,8	X	Y
14 [c]	H	H	8.9	32.0	210.8	64.6	33.0	54.9	42.7	/	/
10	H	CH_3	9.3	33.1	211.0	65.0	38.6	59.6	38.9	/	16.8
1	H	CH_3	9.3	33.1	211.2	65.0	38.9	59.8	a	/	16.8
11 [c]	CH_3	H	8.9	31.8	210.9	68.8	32.5	62.8	44.0	14.4	/
12 [c]	CH_3	CH_3	9.1	32.7	210.3	63.4	35.3	69.9	$<^{40.8}_{41.5}>$	10.4	b
13 [c]	CH_3	CH_3	8.9	33.7	210.6	66.9	39.3	71.3	$<^{37.8}_{41.2}>$	14.0	15.6

[a] Absence of Nuclear Overhauser Enhancement (N.O.E.) in addition to quadrupolar couplings results in broad signals of low intensity which cannot be discriminated from the noise.

[b] Broad signal which cannot be resolved from the signal of X.

[c] Measured at 0.25 M.

[d] Measured at 0.125 M.

tion of the modifications observed for 1 could account for the existence of conformer b, a solvent study carried out on 10 hydrochloride and the corresponding free base showed that in every case the ^{13}C-chemical shifts of the carbonyl carbon were higher for the hydrochloride, and always higher in deuteriomethanol than in aprotic solvents (table 8).

This revealed that 10 behaves as a normal ketone in that hydrogen bonds formed at the level of the carbonyl resulted in deshielding shifts (18). Moreover, a study carried out on 12 and 13 showed a chemical shift difference $\Delta\delta$ of 0.3 ppm in the expected (up -

Table 8. Solvent effect observed on 10.HCl and 10.free base at 0.25 M. ^{13}C chemical shifts of the carbonyl carbon.

Solvent	*10.free base*	*10.HCl*
C_6D_{12}	207.4	/
$CDCl_3$	209.9	210.8
CD_3CN	210.6	211.7
CH_3OD	213.3	214.7
D_2O	/	215.3

field) direction for the carbonyl carbon (table 7). Indeed, the threo species is more homogeneous and merely resides in the pseudo-cyclic state. This conclusion was established on the basis of ^1H-NMR data (24,25) and finds additional support in the fact that an averaged chemical shift is found for the X and Y carbons in 12 while individual resonances are observed for the same carbons in 13. Such a dichotomic situation allows to evaluate the extent of the $\Delta\delta$. The 0.2 ppm $\Delta\delta$ value (carbon 3) measured for 10 and 1 appears therefore to be of the same order. Conclusively, the present results indicate that the base strengthening effect of deuterium just observed for 1 could be the result of the higher positive inductive effect produced by the deuteriomethyl groups (in Halevi's simplification (26)) and the higher stability of the conjugated acid form would in turn favour the pseudo-cyclic conformer.

It should be noted however that in the present state of this research, the ^{13}C-NMR data obtained in the 50-125 mM range can be interpreted on the basis of either a pseudo-cyclic conformer (b) or a dimeric species involving the mutual interaction of the carbonyl and dimethylammonium moieties.

III. IN VITRO AND IN VIVO BIOLOGICAL EVALUATION IN THE RAT AND MOUSE

The in vitro binding test on rat brain preparations did not evidence any significant difference in the inhibitory potency (IC_{50} for 1 : 2.59 ± 0.48 X 10^{-8} M, for 10 : 2.00 ± 0.12 X 10^{-8} M ; sufentanil was employed as the displaced tritiated ligand).

The antinociceptive activity of 1 was assayed in the hot-plate test (27) (ED_{50} 0.77 mg/kg in mice). This value was not significantly different from that observed for methadone (0.80 mg/kg). However, as it was anticipated in the early stage of this research, the duration of action was significantly prolonged [for 1: onset: 8 min, peak: 23 min, duration: 116 min ; for 10 : 10, 23 and 70 min respectively]. These data can be explained on the basis of the differences in the pharmacokinetic parameters measured for 1 ($t_{1/2}$ 233.5 ± 17.4 min, Cl 20.74 ± 0.37 ml/min/kg) and 10 ($t_{1/2}$ 140.5 ± 10.3 min, Cl 32.66 ± 0.93 ml/min/kg) after intravenous injection of 1.5 mg/kg in the rat.

Moreover, a comparative metabolism study of 1 and 10 in the rat clearly demonstrated that the N-demethylation process was considerably depressed, as evidenced by the quantitation of the pyrrolidine metabolite, the major metabolite of methadone (28). The pyrrolidine derivative represents in the urine and in the bile 0.34 and 25.42% of the total metabolites of 1, while respective figures of 5.2 and 31.59% are found for 10. Conversely, the para-hydroxylation route was comparatively enhanced for 1 (29). These results involving a net metabolic switching confirm the expectations formulated in the introduction.

IV. CONCLUSION

The introduction of ditrideuteriomethyl moiety on the 4,4-diphenyl-3-heptanone skeleton of methadone provides a derivative, which

is recognized by the opioid receptor with an efficiency identical to that of methadone. It is noteworthy however that the longer duration of action and the metabolic switching observed for 1 derive from the expected primary isotope effect while the higher basicity and the divergent conformational behaviour in solution remain virtually silent. This is not surprising in view of existing precedences in the literature (24,25). For example, methadone and isomethadone have different pKa values and conformational features, still they exhibit rather similar IC_{50} and ED_{50}. Such a situation reflects the complexity of the opioid receptor for which slight changes of the agonist structure may induce compensating shifts in μ/δ character, resulting in a similar in vivo activity.

V. EXPERIMENTAL SECTION

Melting points were determined with Thomas-Hoover capillary melting point apparatus and are corrected. Differential thermal analysis spectra were obtained from a Perkin-Elmer DSC-2C apparatus. The NMR spectra were recorded on a WP-80/SY Bruker spectrometer ; chemical shifts were measured in ppm downfield from an internal reference of TMS. The probe temperature was kept at 307°K and was monitored with the variable temperature control unit. Mass spectra were obtained from a LKB 9000 S coupled spectrometer using the direct way of simple introduction (70 eV).

(R,S)-2,2-Diphenyl-4-ditrideuteriomethylaminopentanenitrile (4)

To a solution of 6 g (68.5 mmol) of 2 dissolved in 3 ml of H_2O was added 2.8 g (70 mmol) of NaOH dissolved in 5 ml of H_2O. Under stirring, a filtered solution of the above mixture was added over 1 h period to 4.77 g (82.2 mmol) of freshly redistilled propylene oxide. After 12 hrs at room temperature, 90 ml of benzene were

added and the reaction mixture was fractionnally distilled. The fractions under 81°C and above 99°C were discarded. The remaining 4.07 g consisting of a mixture of isomeric aminoalcohols 5 and 6 were dissolved in 25 ml of dry $CHCl_3$ (ethanol free) and treated by 13.4 g (113 mmol) of freshly redistilled thionyl chloride. The reaction mixture was stirred and heated at 55°C for 2 hrs. After evaporating the solvent under reduced pressure, a residue weighing 5.42 g consisting of a mixture of isomeric β-chloroamines 7 and 8 was obtained. Then, to a solution of 6 g (31 mmol) of diphenylacetonitrile and 0.2 g of dibenzo-18-crown-6 in 6 ml of DMSO were added under stirring 5 g (125 mmol) of sodium hydroxyde in 5 ml of distilled water in one portion and 5.42 g of 7 and 8 over one hour period. The reaction mixture was gradually heated up to 70°C and this temperature was maintained for 3 h. After cooling, the basis fraction was isolated in the usual way (6) and recrystallized from n-hexane and then from n-heptane to yield 2.8 g (32.5%) of 4, mp 81-82°C.

This material was pure in GLC. MS m/e 284 (15.5%), 266 (10%), 192 (42%), 165 (18%), 78 (100%).

(R,S)-4,4-Diphenyl-6-ditrideuteriomethylamino-3-heptanone hydrochloride (1)

This material was synthesized according to the procedure described by BOCKMUHL and EHRHARDT (3). To a suspension of 0.24 g (10 mmol) of magnesium in 5 ml of dry diethylether was added 2.55 g (23 mmol) of ethyl bromide. After completion of the reaction, a solution of 2.8 g (9.86 mmol) of 4 in 3 ml of dry xylene was added to the reaction mixture under stirring. The diethylether was distilled off in dry conditions; the reaction mixture was heated under reflux for 1 h and then decomposed with 100 ml of 8 N hydrochloric acid. After the usual work up (3), 2.48 g (79%) of 1 were obtained. The hydrochloride crystallized from ethanolic hydrochlo-

ric acid was obtained in 72% yield. It was recrystallized from isopropanol to constant melting point (mp 233°C).
This product was pure in GLC and HPTLC. MS m/e 315 (2.5%), 300 (21.5%), 223 (19%), 78 (100%). Deuterium content : 98%. Other parameters are listed in tables 1 and 2.

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REFERENCES

1. Gérardy B.M., Poupaert J.H. and Dumont P. - Bull. Soc. Chim. Belg. 90:977-980 (1981)
2. Baillie T.A. - Pharmacological Reviews 33:81-132 (1981)
3. Bockmühl M. and Ehrhardt G. - J. Liebigs Ann. Chem. 561:52-85 (1949)
4. Henkel J.G., Berg E.P. and Portoghese P.S. - J. Med. Chem. 19: 1308-1314 (1976)
5. Easton N.R., Gardner J.H. and Stevens J.R. - J. Am. Chem. Soc. 69:2941 (1947)
6. Poupaert J.H., Van der Jeugd P., Gérardy B.M., Claesen M. and Dumont P. - J. Chem. Research (M):2484-2492 (1981)
7. Walton E., Ofner P. and Thorp R.H. - J. Chem. Soc.:648-655 (1949)
8. The Merck Index, Ninth Edition - Merck and CO., Inc.; Rahway, N.J., U.S.A.; p.774 (1976)

9. DIRDIF : Direct methods for difference structures. Beurskens P.T., Bosman W.P., Doesburg H.M., Gould R.O., Van den Hark Th.E.M., Prick P.A.J., Noordik J.H., Beurskens G. and Prthasarathi V. - Technical Report 1981/2, Crystallography Laboratory, Toernooiveld, 6525 ED Nijmegem, Netherlands
10. SHELX 76 : Program for Crystal Structure Determination. Sheldrick G.M. (1976), University of Cambridge, England
11. Hanson A.W. and Ahmed F.R. - Acta Cryst. 11:724-728 (1958)
12. Elison C., Rapoport H., Laursen R., Elliott H.W. - Science 134:1078-1079 (1961)
13. Heck H.D'A., Simon R.L. and Anbar M. - J. Chromatogr. 133:281-290 (1977)
14. Henkel J.G., Bell K.H. and Portoghese P.S. - J. Med. Chem. 17: 124-129 (1974)
15. Portoghese P.S. - Acc. Chem. Res. 11:21-29 (1978)
16. Loew G.H., Berkowitz D.S. and Newth R.C. - J. Med. Chem. 19: 863-869 (1976)
17. Froimowitz M. - J. Med. Chem. 25:689-696 (1982)
18. Levy G.C., Lichter R.L., Nelson G.L. - Carbon-13 Nuclear Magnetic Resonance Spectroscopy, 2nd edition, Wiley and Sons, New-York (1980)
19. Berger S. and Kunzer H. - Angew. Chem. 95:321-322 (1983)
20. Hansen P.E. and Led J.J. - J. Org. Magn. Res. 15:288-293 (1981)
21. Anet F.A.L., Basus V.J., Hewett A.P.W. and Saunders M.J. - J. Am. Chem. Soc. 102:3945-3946 (1980)
22. Kurobane I., Vining L.C., McInnes A.G. - Tetrahedron Lett. 4633-4636 (1978)
23. O'Brien D.H. and Stipanovic R.D. - J. Org. Chem. 43:1105-1111 (1978)
24. Henkel J.G., Berg E.P. and Portoghese P.S. - J. Med. Chem. 19: 1308-1314 (1976)
25. Portoghese P.S., Poupaert J.H., Larson D.L., Groutas W.C., Meitzner G.D., Swenson D.C., Smith G.D. and Duax W.L. - J. Med. Chem. 24:684-688 (1982)
26. Halevi E.A., Nussim M. and Ron A. - J. Chem. Soc.:866 (1963)
27. Atwell L. and Jacobson A.E. - Lab. Anim. 7:42-47 (1978)
28. Jacob P., Rigod J.F., Pond S.M. and Benowitz N.L. - J. Anal. Toxicol. 5:292-295 (1981)
29. Gérardy B.M., Poupaert J.H., Kapusta D., Vandervorst D. and Dumont P. - Unpublished results