Diethyl 1-(1,1-Diphenyl-3-dialkylaminopropyl)phosphonate (8). Two methods were used to synthesize these compounds. The first method was identical with the procedure used to prepare 7 described previously. The hydrochloride did not precipitate and had to be isolated in a conventional acid-base extraction and the hydrochloride was prepared by passing hydrogen chloride gas through an ether solution of the basic material isolated from the reaction. In the second procedure a solution of 0.02 mol of diethyl benzyldiarylphosphonate (prepared by the method of Smith and Burger[10]) and 0.03 mol of potassium *tert*-butoxide in dry benzene was stirred at room temperature for 15 min. The dried toluene extract of the chloroalkylamine was added and the solution refluxed overnight. The reaction mixture was worked up in the conventional manner and the compounds prepared by this method are described in Table II.

Pharmacology. The LD_{50} determination was conducted utilizing a minimum of five 25–30 g male Swiss-Webster strain mice in each of at least five groups. The drugs were administered in a phosphate buffer (Sorensen pH 4.7) or in distilled water. Animals of each dosage level were given the drug intraperitoneally and placed in observation cages for 24 hr. Death was observed to occur within 15 min after administration of the drug or the animal survived. The recorded data were analyzed by a probit method developed by Litchfield and Wilcoxon[11] and adapted for use in a computer by W. H. S. The results of the toxicity experiments are given in Tables III and IV.

The ED_{50} for the hot-plate method was determined using essentially the method of Eddy and Leimbach.[12] The hot plate used was a metal cup immersed in a constant temperature water bath maintained at 55°. The mouse was placed on the hot plate and a stop watch started. The time needed for the mouse to react to the heat was recorded. The end point occurred when the mouse licked a front foot or attempted to alternately hold its hind feet in the air. The reaction time was determined at 5, 10, 20, 30, 45, and 60 min after the animal received the drug. The area of the reaction time–time after drug curve was determined by means of a computer program utilizing the reaction times recorded. The average for 100 control animals was 401.9 sec-min with a standard deviation of 41.2 sec-min. For the drug testing, the animals were tested for consistency of their reaction and if these times were consistent, the drug was administered intraperitoneally. After 15 min the reaction times of the mouse were determined at the specified periods and the area of the curve was computed. An animal was judged to show analgesia if the area of his reaction time curve exceeded that of the control by more than two standard deviations. Ten animals were used at each dosage level and five dosage levels were used for each drug. The ED_{50} was calculated by the same computer program used for the LD_{50} experiments. The results for the hot-plate ED_{50} experiments are found in Tables III and IV.

The acetic acid writhing ED_{50} study utilized the technique developed by Koster.[13] The drug was administered subcutaneously to five groups of ten mice for each drug. After 15 min the animals were challenged with a dose of 60 mg/kg of 0.6% acetic acid administered intraperitoneally. The animals were observed for 30 min. Animals showing obvious writhing were recorded as not showing analgesia and those which showed no writhing were recorded as showing analgesia. The per cent of animals showing analgesia was recorded and these data were used for the calculation of the ED_{50} using the previously described computer program. The results of the acetic acid writhing test are found in Tables III and IV.

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Stereochemical Studies on Medicinal Agents. 16.[1] Conformational Studies of Methadone and Isomethadone Utilizing Circular Dichroism and Proton Magnetic Resonance

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The solution conformations of methadone (1), isomethadone (2), and their respective HCl and MeI salts have been investigated using CD and nmr. The fact that the sign of the Cotton effect of 1 undergoes solvent-induced inversion in CH_3OH (compared to hexane and $CHCl_3$) while 2 or salts of 1 and 2 show no such change suggests that 1 exhibits a high degree of conformational mobility compared to 2. When dissolved in CD_3OD, only 1 was found to undergo a rapid intramolecularly catalyzed proton exchange, thus suggesting the presence of a significant population of conformers **1a** and **1c**. Conformational analysis based on the C-5,6 vicinal coupling constants indicated approximately a 1:1:2 ratio of the three possible staggered conformations of 1 in $CDCl_3$. A perturbation of this distribution occurred in CD_3OD. This behavior was not observed in the case of 2 and its derivatives, and this is consistent with a much higher degree of conformational homogeneity in 2. In the case of 2, nmr analysis together with other data suggests that **2b** is the predominant rotamer. It is proposed that the higher enantiomeric (−/+) analgetic potency ratio of 2 relative to 1 may in part be related to their difference in conformational flexibility. On this basis it is suggested that 2 might possess more selective action than 1 and might be worthy of investigation as a suitable alternative to 1 in the maintenance of addicts.

The conformations of the narcotic analgetics, methadone (1)[2,3] and isomethadone (2),[3] have been the subjects of considerable stereochemical investigation,[4-10] as these positional isomers differ from many other types of narcotic analgetics in their formal degree of conformational flexibility. As early as 1954, Beckett and Casy[4] suggested that these compounds possessed a preferred conformation which was postulated to fit a hypothetical receptor site.

† This paper is dedicated to Professor Alfred Burger in recognition of his many accomplishments in the field of medicinal chemistry.

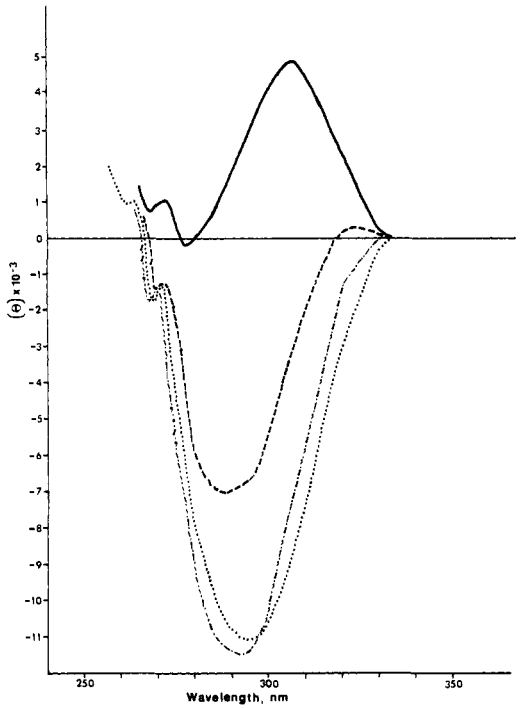


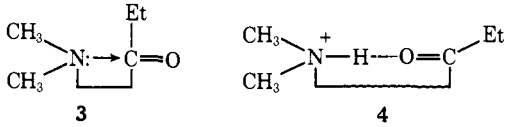
Figure 1. CD spectra of (+)-(6*S*)-methadone (**1**): 0.1% solutions in CH_3OH (———), $CHCl_3$ (– – – –), hexane (·····), and CH_3CN (–·–·–·).

Two such conformations are schematically illustrated by **3** and **4**. As the free base, a N→C=O interaction was postulated (**3**), while the protonated form was thought to possess the internally hydrogen-bonded structure **4**. No direct evidence has appeared either supporting or refuting the existence of **3** or **4** in solution, although some indirect evidence is available. The abnormally high pK_a of **1** compared to that of **2** and the deoxy analog of methadone has been interpreted[6] in terms of stabilization of the conjugate acid by intramolecular hydrogen bonding of the ammonium hydrogen with the carbonyl oxygen (**4**), while a similar stabilized cyclic conformation for the conjugate acid of isomethadone was thought not to be favored because of steric effects.[7] However, an X-ray crystallographic study[8] of (+)-methadone hydrobromide (**1**·HBr) failed to show intramolecular H bonding in the crystalline state. On the basis of nmr studies,[9,10] Casy has proposed an internally associated conformation for methadone base in $CDCl_3$[10] which involves an interaction of the type postulated in **3**. This conclusion was reached solely on the basis of the higher than expected chemical shift of the secondary methyl due to a postulated shielding by one of the phenyl groups. However, in view of the complexity of the molecule and the possibility that such shielding may arise from another source, this interpretation would benefit from corroborative evidence.

$CH_3CH_2COCPh_2CHRCHR'NMe_2$

1, R = H; R′ = CH_3

2, R = CH_3; R′ = H



3

4

It was felt that the application of circular dichroism (CD) and nmr analysis utilizing the C-5,6 vicinal coupling constants would serve as a basis for further investigation of the conformations of **1** and **2** and their derivatives in solution. Utilizing these techniques we now present evidence which suggests that there are substantial conformational differences between **1** and **2**.

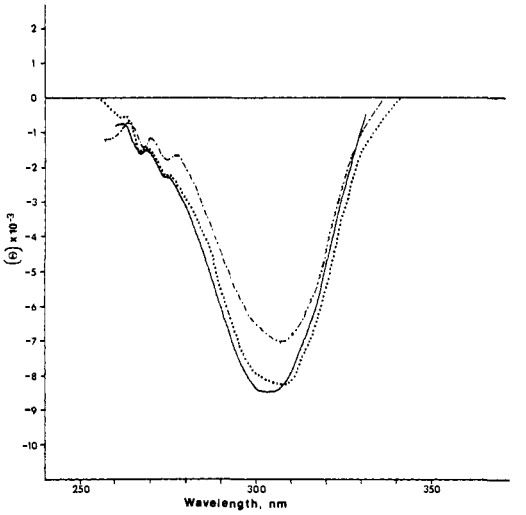


Figure 2. CD spectra of (−)-(5*S*)-isomethadone (**2**): 0.1% solutions in CH_3OH (———), $CHCl_3$ (–·–·–·), and hexane (·····).

CD Studies. It is known[11,12] that changes in the orientation of a chiral center with respect to a carbonyl group in a molecule can alter the magnitude of the observed Cotton effect. If this change is large enough, an actual reversal of sign is noted. It follows then that changes in the conformational equilibrium of optically active **1** and **2** will similarly affect the magnitude and sign of the observed CD curves. One way to initiate changes in conformational distribution would be through the use of solvents of differing polarity. In nonpolar solvent such as hexane, intramolecular forces may be of primary importance, while in more polar solvent such as methanol, intermolecular solute–solvent interactions can become significant.

The CD spectra of (+)-(6*S*)-methadone and (−)-(5*S*)-isomethadone in different solvents are shown in Figures 1 and 2, respectively. Each spectrum shows the n → π* carbonyl transition at 290–310 nm and the ^1L_b aromatic transition with fine structure at 260–275 nm. Particularly striking is the reversal of the sign of the Cotton effect of the carbonyl transition of **1** in methanol. Since the CD curve of a flexible molecule such as **1** represents a weighted average of the optical activity of each conformation, the reversal of sign of the Cotton effect suggests a different conformational population for methadone base in MeOH. Interestingly, the CD spectrum in CH_3CN shows no change in the sign of the Cotton effect when compared to spectra obtained in other nonhydroxylic solvents, although its dielectric constant is greater than that of methanol. This result indicates that the perturbation in conformational distribution observed for **1** is due primarily to hydrogen bonding of the solvent to the amine function and perhaps to the carbonyl group. In the case of **2** (Figure 2), no appreciable change in the sign or magnitude of the CD curve was noted, suggesting that no significant change in the conformational population occurs. This is consistent with the previous suggestion[7] that isomethadone possesses considerably greater conformational homogeneity than methadone and that intramolecular association (either as the base or salt) is unfavorable due to steric effects.

In order to evaluate the effects of the basic nitrogen atom in **1** and **2** on the Cotton effect, both were converted to their respective methiodide salts. Their CD spectra (Figure 3) showed no appreciable solvent-dependent change in the sign or magnitude of the Cotton effect. In these cases, the nitrogen function no longer has a lone pair

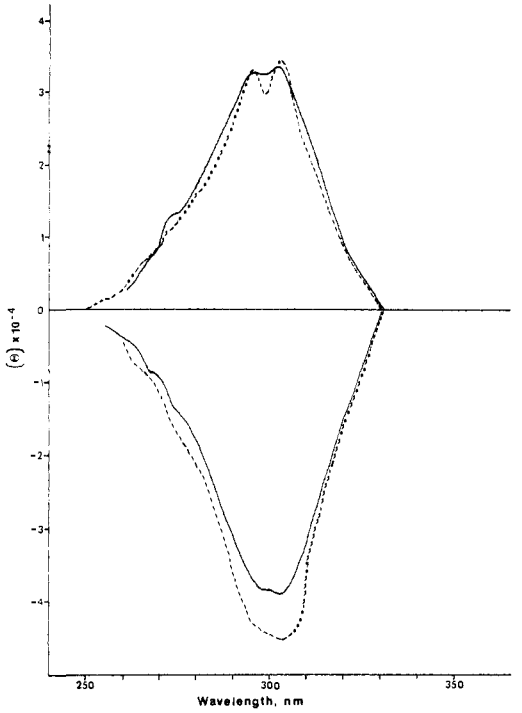


Figure 3. CD spectra of (+)-(6S)-methadone methiodide (1·CH_3I) above and (−)-(5S)-isomethadone methiodide (2·CH_3I) below: 0.1% solutions in CH_3OH (———) and $CHCl_3$ (-----).

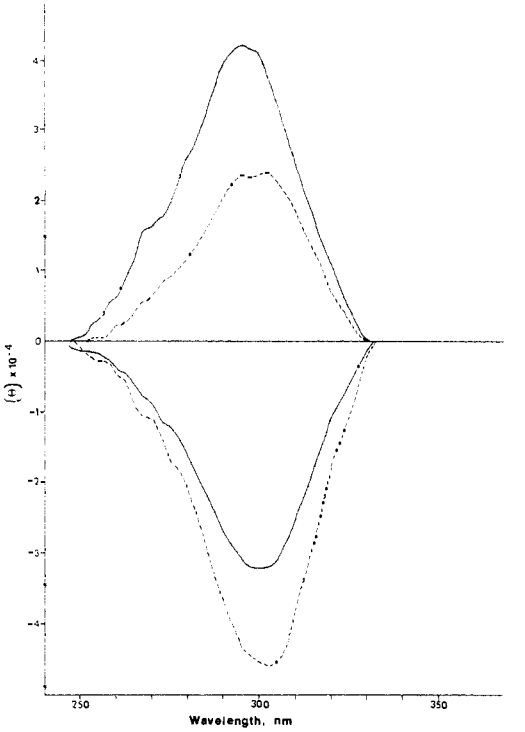
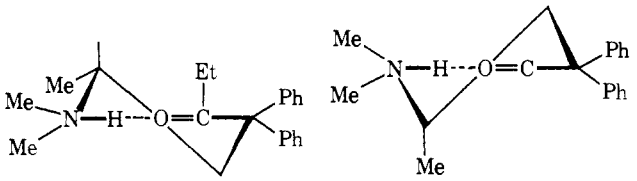


Figure 4. CD spectra of (+)-(6S)-methadone hydrochloride (1·HCl) above and (−)-(5S)-isomethadone hydrochloride (2·HCl) below: 0.025% solutions in CH_3OH (———) and $CHCl_3$ (-----).

of electrons to interact with the carbonyl group, thereby precluding a cyclic conformation such as that shown in **3**. Also contributing to the difference between the preferred conformations in **1** and **1**·CH_3I is the additional steric bulk of the substituents around the nitrogen, thereby favoring an antiperiplanar conformation in the latter.

The CD curves of **1**·HCl and **2**·HCl in $CHCl_3$ and CH_3OH are shown in Figure 4. It can be noted that both curves are of the same sign, but **1**·HCl shows a significantly reduced intensity in $CHCl_3$ compared to CH_3OH. This reduction may reflect a solvent-induced change in the mole fractions of two or more internally associated rotamers such as **5a** and **5b**.



5a **5b**

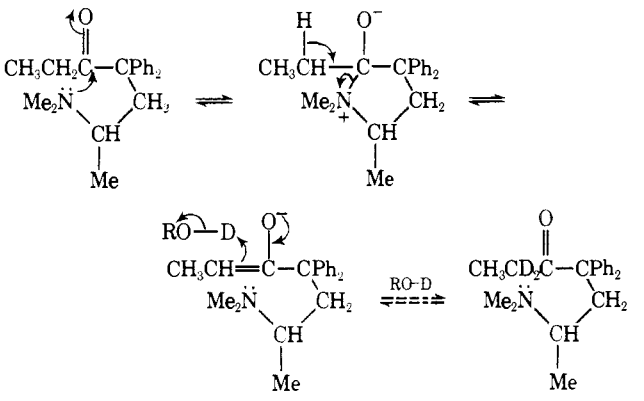
Nmr Studies. When methadone base was placed in CD_3OD, a rapid proton exchange at the C-2 position occurred to afford the α-dideuterated product **6**. The rate of

$CH_3CD_2COCPh_2CH_2CHMeNMe_2$

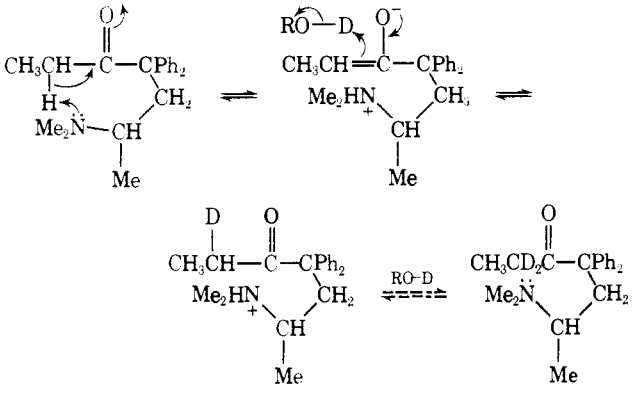
6

this reaction was measured by following the change in shape of the adjacent methyl signal at two concentrations, 0.65 and 0.03 *M*. Within experimental error, the half-life for exchange (3.4 min) was found to be concentration independent, indicating that the exchange process is intramolecularly catalyzed. There are two possible mechanisms which may be responsible for promoting this rapid exchange, and both require a conformation which brings the amine function into close proximity with either the carbonyl group (mechanism 1) or with the α-methylene group (mechanism 2). The first mechanism involves base-promoted enolization as a consequence of a N→C=O interaction, while the alternative process affords the same result by direct abstraction of the C-2 proton. No evidence was obtained to support one process over the other, and arguments can be made in favor of both under these conditions. As expected, salts of **1** showed no tendency to undergo exchange, further emphasizing the role of the basic nitrogen.

mechanism 1



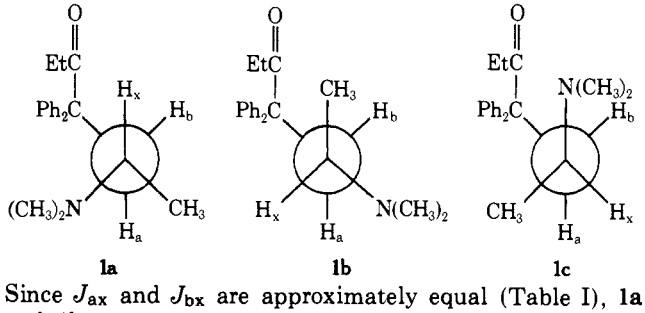
mechanism 2



A very slow exchange reaction was also observed for isomethadone base (2) in CD_3OD which was estimated to be at least two orders of magnitude slower than **1**. The slowness of exchange may mean that it is intermolecularly catalyzed. This is consistent with a preferred antiperiplanar conformation for **2**[7] which is incapable of internal association. Again 2·DCl and 2·CH_3I exhibited no exchange in CD_3OD.

In order to simplify the nmr spectra, the C-2 protons of 1 and 2 were exchanged in a mixture of D_2O, NaOD, and DMSO-d_6 to afford the dideuterated bases. These compounds then were converted to the respective methiodide derivatives and DCl salts. Although small chemical shift differences were noted for 1 and 2 in $CDCl_3$ and CD_3OD, the C-5,6 vicinal coupling constants proved to be a more reliable measure of net conformational changes within each molecule since these are known to be constant with solvent variation.[13] Thus, changes in the coupling constants with varying solvent polarity were determined for 1, 2, and their respective derivatives (Table I). Unfortunately, chemical shift overlap and line broadening prevented the determination of both coupling constants in the salts, but sufficient information was obtained from the visible couplings to draw several meaningful conclusions. The following analyses were based on two approximations: (1) only staggered conformations about the C(5)–C(6) bond were considered to contribute to the observed coupling constants, and (2) all antiperiplanar vicinal coupling constants were considered to be of equal magnitude throughout the entire series (approximately 13.5 Hz); similarly all gauche constants were considered to be about 2.5 Hz. These constants, based on a family of curves described by the Karplus equation,[14] are representative of the general range of observed values and were compared for internal consistency with the magnitude of the observed J_{vic}'s for 1 and 2 and derivatives. The magnitudes were also in general agreement with those observed for amphetamine and related compounds.[15]

Newman projections of the three staggered conformations of 1 about the C-5,6 bond are shown as **1a–c**. It should be noted that H_a and H_b are assigned arbitrarily, with no absolute assignment implied. Rotamer **1a** will contribute a large J_{ax} and a small J_{bx}, while 1b will produce a small J_{ax} and a large J_{bx}. Conformer **1c** would be expected to produce both a small J_{ax} and a small J_{bx}.



1a **1b** **1c**

Since J_{ax} and J_{bx} are approximately equal (Table I), **1a** and 1b must contribute nearly equally to the conformational population in $CDCl_3$. Assigning the previously defined values for J_{anti} and J_{gauche}, it is predicted by the relationship

$$J_{obsd} = \sum_i J_i p_i$$

and the normalization condition

$$\sum_i p_i = 1$$

where J represents the coupling constant in the ith environment and p the fraction of protons in that environment, that the respective rotamers are present in approximately a 1:1:2 ratio (26:27:47) in $CDCl_3$. In CD_3OD, J_{ax} and J_{bx} are no longer equal; hence **1a** and 1b no longer contribute equally to J_{obsd}. Analysis as above disclosed that a rotameric distribution of approximately 10:41:49 is present, and that either **1a** or 1b increases at the expense of the other. The persistence of the double gauche rotamer **1c** in both solvents is somewhat surprising in light of the considerable steric interactions which must be present in **1c**. Both **1a** and **1c** are capable of internal association, and the preference for **1c** over **1a** might involve significant solvation effects. Since it is generally known that increasingly polar solvents tend to diminish the magnitude of intramolecular association, it is possible to speculate that in the case of 1, rotamer 1b increases at the expense of **1a**. However, without actual assignments for H_a and H_b, no unequivocal interpretation can be made.

Table I. Nmr Data for Methadone, Isomethadone, and Derivatives

Compd	Solvent	Chemical shift, δ[a] H_a	H_b	H_x	J_{ax}, Hz	J_{bx}, Hz
1	$CDCl_3$	1.99	2.87	2.37	5.5[b]	5.4[b]
	CD_3OD	2.13	2.82	2.34	3.6	7.0
1·DCl	$CDCl_3$	2.22	3.05	3.2	*d*	9.7
	CD_3OD	2.18	3.1	3.2	*d*	7.8
1·CH_3I	$CDCl_3$	2.20	3.15	3.4	*d*	9.3
	CD_3OD	2.26	3.2	3.4	*d*	9.3
2	$CDCl_3$	1.47	2.18	3.32	2.5[c]	10.3[c]
	CD_3OD	1.49	2.24	3.36	2.5	10.8
2·DCl	$CDCl_3$	1.89	3.12	3.50	*d*	11.4
	CD_3OD	2.11	3.29	3.61	*d*	9.7
2·CH_3I	$CDCl_3$	2.30	3.45	3.7	*d*	8.4
	CD_3OD	2.33	3.55	3.8	*d*	8.3

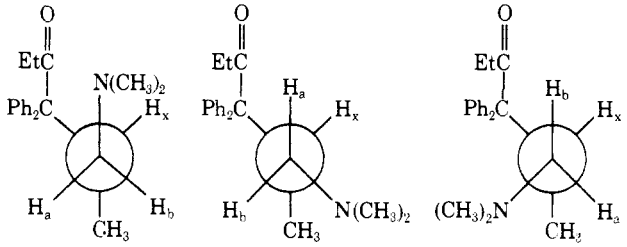
[a] H_a and H_b correspond to the C-5 or C-6 methylene in methadone and in isomethadone and are assigned arbitrarily. [b] Literature value, 5 Hz [R. Rümmler and R. Haller, *Pharmazie*, **26**, 28 (1971)]. [c] Literature value for J_{ax} and J_{bx}, 4 and 10.5 Hz [R. Haller and R. Rümmler, *Arch. Pharm. (Weinheim)*, **303**, 775 (1970)]. [d] Chemical Shift overlap and line broadening prevent assignment.

The most important point to be made on the basis of the nmr data for 1 is that it possesses an unusually high degree of conformational mobility and sensitivity to solvent perturbation. It follows that while N→C=O internal association very likely is present in the molecule, it certainly does not predominate to the exclusion of the unassociated conformer 1b.

It is noteworthy that after this work was completed, X-ray analysis of methadone base‡ revealed the presence of an N→C=O interaction with a conformation in the crystal lattice which corresponds to rotamer **1a**. While this result is in harmony with our study, one must proceed cautiously in any attempted extrapolation to solution phenomena because of the conformational mobility of methadone and the sensitivity of the rotameric population to solvent-induced conformational changes.

The analysis of the spectra of isomethadone base (2) produced somewhat different results, in that both large and small vicinal couplings were observed (Table I). In fact, the large value of J_{bx} indicates that one of the rotamers (**2a** or 2b) actually is favored almost exclusively over the other, with **2c** contributing somewhat less (assuming staggered conformations). Of the two possible rotamers which are consistent with these coupling constants, 2b seems more reasonable because its gauche interactions should be of lower energy if one uses steric size as a criterion. This also receives support from our present deuterium exhange study and from pK_a studies[7] which suggest the extended conformer 2b of the conjugate acid to predominate. Significantly, no appreciable change in J

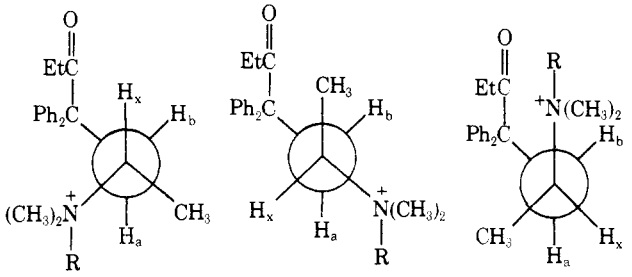
‡ E. Shefter, private communication.



2a 2b 2c

values was noted when the solvent was changed.

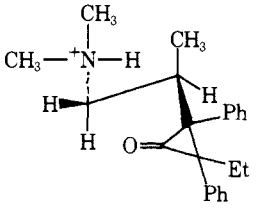
Analysis of the salts of 1 and 2 (Table I) was made more difficult by the overlap and broadening of some of the proton absorptions. In the case of methadone DCl (1·DCl), the large coupling in $CDCl_3$ is indicative of a population distribution somewhat different from that of methadone base. For a value of 9.7 Hz, the mole fractions of **7a** and 7b must obviously be quite different, and on the basis of the previous pK_a evidence[6] it is suggested that **7a** (R = D) is the preferred conformation. In the absence of the other coupling constant, no estimate of the relative populations of each rotamer could be made, however. In methanol, the 7.8-Hz coupling value could reflect an increase in the contribution of **7c** if it is assumed that both conformers are internally hydrogen bonded in the form of the conjugate acid as illustrated in **5a** and **5b**.[6]



7a 7b 7c

The coupling data for methadone methiodide (1·CH_3I) are essentially unchanged in $CDCl_3$ and CD_3OD. The one visible coupling constant (9.3 Hz) is consistent with a conformational population that is largely antiperiplanar for the protons involved. It is reasonable that 7b (R = CH_3) is favored over 7a (R = CH_3) since the bulky quaternary ammonium and quaternary carbon groups would be expected to prefer an antiperiplanar orientation over a gauche relationship. The much greater stability of this rotamer (7b) is consistent with the lack of change in the observed coupling constants and constancy of the CD spectra when determined in different solvents.

Finally, isomethadone derivatives 2·DCl and 2·CH_3I both show vicinal couplings which reflect predominantly an antiperiplanar relationship for the protons involved. In the case of 2·DCl, the magnitude is similar to that of the corresponding coupling constant in the parent compound. From this, as well as the uniformity of the CD spectra, the observed lower pK_a of 2, and the conformational arguments expressed in this paper and in an earlier communication,[7] it seems reasonable that the salt should have a preferred conformation similar to that of the parent compound represented by the unassociated rotamer **2b**. The proposed conformational preference for isomethadone deuterium chloride is depicted by perspective formula **8**. It is believed that the molecule is restricted primarily to this conformation for reasons discussed previously.[7] For 2·CH_3I, the lower value of J_{bx} may be the result of an off-staggered conformation due to steric crowding.



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Summary and Conclusions

These studies and previous evidence[6,7] suggest that methadone is a much more flexible molecule than isomethadone and that each exists in a substantially different preferred conformation in solution. Further, N→C=O interaction seems to occur only in methadone, and the magnitude of this interaction is considerably weaker than was generally believed. The existence of an internally stabilized structure[6] (**5a** ⇄ 5b) for the conjugate acid of methadone is consistent with the present results as well. In contrast, isomethadone exists predominantly in an extended conformation (2b) either as the salt or the free base.

The greater conformational homogeneity of isomethadone might possibly be the cause of the twofold greater enantiomeric (−/+) analgetic potency ratio[6,7,16] of isomethadone over methadone. Moreover, it is noteworthy that to date there have been no reports of observed inversion of receptor stereoselectivity in the isomethadone series, while such inversions are known to occur in the methadone series.[7,16] Thus, the results reported here tend to support the suggestion that the greater conformational flexibility of methadone provides a wider range of binding modes at the receptor site than does isomethadone. In view of these differing conformational flexibilities, isomethadone might be worthy of investigation as an alternative to methadone in the maintenance of heroin addicts in the hope that its conformational homogeneity might afford greater selectivity of action.

Experimental Section

CD spectra were measured at ambient temperature with a Cary 60 spectrometer using 0.025–0.1% (wt/v) solutions in a 1-cm cell. Nmr spectra were determined on a Varian XL-100 spectrometer as 10–15% solutions in $CDCl_3$ and CD_3OD (TMS) at 29°.

The compounds used in the CD study were obtained from commercially available (+)-1·HCl and (−)-2·HCl by standard methods and purified to reported[17] physical constants.

Methadone-2-d_2. Methadone base (1.0 g) derived from 1·HCl was treated twice with D_2O (10 g) which had been reacted with 100 mg of Na. The mixture was heated at reflux for 1 hr, followed by extraction with Et_2O and recrystallization from 30–60° petroleum ether. A portion was converted to the DCl salt by treatment with excess 25% DCl in D_2O, followed by evaporation to dryness *in vacuo*. The methiodide salt was synthesized by the standard method. Nmr analysis showed complete exchange.

Isomethadone-2-d_2. Isomethadone (1.0 g) was treated with D_2O (15 g) which had been reacted with 150 mg of Na. DMSO-d_6 (10 ml) was added to the mixture to promote solubility and the solution heated at 100° for 1 hr. The deuterated product was extracted with Et_2O, dried over $MgSO_4$, evaporated, and distilled. The DCl and methiodide salts were prepared as above. Nmr analysis indicated complete exchange.

Exchange Rate Studies. Methadone (100 mg) was introduced into an nmr tube and dissolved in a drop of $CDCl_3$. After placement in the nmr probe, enough CD_3OD (0.5 ml) was injected into the tube to bring the concentration to 0.65 *M*. The region of the methyl resonance at δ 0.5 was repeatedly scanned at 1-min intervals, each scan lasting *ca.* 10 sec. The exchange rate constant was obtained by following the collapse of the triplet signal; the rate constant was $k = 3.4 \pm 0.7 \times 10^{-3}$ sec^{-1} ($t_{1/2}$ = 3.4 ± 0.9 min).

The exchange rate at 0.03 *M* was conducted by dissolving methadone (5 mg) in 1 drop of $CDCl_3$ in an nmr tube and scanning immediately after injection of CD_3OD (0.5 ml), using pulsed FT mode. One hundred scans were accumulated per plot of the signal, with a 40-μsec pulse and a 1-sec aquisition time. k = 2.66

$\times 10^{-3}$ sec^{-1} ($t_{1/2}$ = 4.3 min).

(+)-(6S)-Methadone (1, **Figure 1**): CD (c 0.1, hexane) $[\theta]_{330}$ −310, $[\theta]_{320}$ −2970, $[\theta]_{310}$ −7180, $[\theta]_{300}$ −10,520, $[\theta]_{294}$ −11,080, $[\theta]_{290}$ −10,077, $[\theta]_{280}$ −7920, $[\theta]_{271}$ −1350, $[\theta]_{269}$ −1390, $[\theta]_{267}$ 0, $[\theta]_{264}$ 1040, $[\theta]_{262}$ 940; CD (c 0.1, $CHCl_3$) $[\theta]_{330}$ 120, $[\theta]_{323}$ 300, $[\theta]_{320}$ 190, $[\theta]_{318}$ 0, $[\theta]_{310}$ −1980, $[\theta]_{300}$ −5320, $[\theta]_{289}$ −6980, $[\theta]_{280}$ −5820, $[\theta]_{272}$ −1240, $[\theta]_{270}$ −1420, $[\theta]_{267}$ 0; CD (c 0.1, CH_3OH) $[\theta]_{330}$ 230, $[\theta]_{320}$ 2320, $[\theta]_{310}$ 4490, $[\theta]_{307}$ 4870, $[\theta]_{300}$ 4100, $[\theta]_{290}$ 1860, $[\theta]_{280}$ 0, $[\theta]_{277}$ −230, $[\theta]_{272}$ +1080, $[\theta]_{268}$ 740, $[\theta]_{265}$ 1480, $[\theta]_{260}$ 1110; CD (c 0.1, CH_3CN) $[\theta]_{330}$ 0, $[\theta]_{320}$ −1240, $[\theta]_{310}$ −5570, $[\theta]_{300}$ −10,090, $[\theta]_{292}$ −11,460, $[\theta]_{290}$ −11,370, $[\theta]_{280}$ −8940, $[\theta]_{271}$ −1485, $[\theta]_{269}$ −1700, $[\theta]_{267}$ 0.

(−)-(5S)-Isomethadone (2, **Figure 2**): CD (c 0.1, hexane) $[\theta]_{340}$ −120, $[\theta]_{330}$ −140, $[\theta]_{320}$ −5250, $[\theta]_{310}$ −8160, $[\theta]_{307}$ −8320, $[\theta]_{300}$ −7950, $[\theta]_{290}$ −5570, $[\theta]_{280}$ −2970, $[\theta]_{275}$ −2220, $[\theta]_{274}$ −2290, $[\theta]_{269}$ −1490, $[\theta]_{266}$ −1560, $[\theta]_{263}$ −500, $[\theta]_{262}$ −580, $[\theta]_{260}$ −460; CD (c 0.1, $CHCl_3$) $[\theta]_{330}$ −920, $[\theta]_{320}$ −4330, $[\theta]_{310}$ −6810, $[\theta]_{307}$ −7010, $[\theta]_{300}$ −6510, $[\theta]_{290}$ −4430, $[\theta]_{280}$ −2050, $[\theta]_{277}$ −1610, $[\theta]_{274}$ −1760, $[\theta]_{270}$ −1130, $[\theta]_{268}$ −1470, $[\theta]_{264}$ −670, $[\theta]_{260}$ −1110; CD (c 0.1, CH_3OH) $[\theta]_{330}$ −870, $[\theta]_{320}$ −4550, $[\theta]_{310}$ −7980, $[\theta]_{275}$ −2350, $[\theta]_{274}$ −2350, $[\theta]_{269}$ −1520, $[\theta]_{267}$ −1630, $[\theta]_{263}$ −870, $[\theta]_{260}$ −930.

(+)-(6S)-Methadone Methyl Iodide (1·CH_3I, **Figure 3**): CD (c 0.1, $CHCl_3$) $[\theta]_{330}$ 300, $[\theta]_{320}$ 8700, $[\theta]_{310}$ 24,600, $[\theta]_{302}$ 33,600, $[\theta]_{299}$ 32,600, $[\theta]_{295}$ 32,700, $[\theta]_{290}$ 28,100, $[\theta]_{280}$ 17,000, $[\theta]_{275}$ 13,300, $[\theta]_{273}$ 12,900, $[\theta]_{270}$ 9000; CD (c 0.1, CH_3OH) $[\theta]_{330}$ 400, $[\theta]_{320}$ 8900, $[\theta]_{310}$ 22,100, $[\theta]_{303}$ 34,700, $[\theta]_{299}$ 29,700, $[\theta]_{295}$ 34,800, $[\theta]_{290}$ 25,900, $[\theta]_{280}$ 16,200, $[\theta]_{274}$ 11,300, $[\theta]_{272}$ 10,800, $[\theta]_{270}$ 8800, $[\theta]_{267}$ 6900, $[\theta]_{266}$ 6800, $[\theta]_{260}$ 2800, $[\theta]_{250}$ 0.

(−)-(5S)-Isomethadone Methyl Iodide (2·CH_3I, **Figure 3**): CD (c 0.1, $CHCl_3$) $[\theta]_{330}$ −1000, [83]$_{320}$ −15,600, $[\theta]_{310}$ −35,800, $[\theta]_{303}$ −45,300, $[\theta]_{295}$ −43,000, $[\theta]_{290}$ −36,300, $[\theta]_{280}$ −21,300, $[\theta]_{275}$ −17,200; CD (c 0.1, CH_3OH) $[\theta]_{330}$ −1100, $[\theta]_{320}$ −14,400, $[\theta]_{310}$ −32,100, $[\theta]_{303}$ −38,800, $[\theta]_{300}$ −38,500, $[\theta]_{297}$ −38,300, $[\theta]_{290}$ −31,400, $[\theta]_{280}$ −18,200, $[\theta]_{274}$ −13,500, $[\theta]_{267}$ −8500, $[\theta]_{261}$ −4100, $[\theta]_{255}$ −2300.

(+)-(6S)-Methadone Hydrochloride (1·HCl, **Figure 4**): CD (c 0.025, $CHCl_3$) $[\theta]_{330}$ 0, $[\theta]_{320}$ 5900, $[\theta]_{310}$ 17,300, $[\theta]_{302}$ 24,000, $[\theta]_{298}$ 23,400, $[\theta]_{295}$ 23,700, $[\theta]_{290}$ 20,400, $[\theta]_{280}$ 11,700, $[\theta]_{275}$ 9100, $[\theta]_{274}$ 8900, $[\theta]_{270}$ 6600, $[\theta]_{268}$ 5700, $[\theta]_{267}$ 5500, $[\theta]_{262}$ 2500, $[\theta]_{260}$ 2300, $[\theta]_{255}$ 600, $[\theta]_{254}$ 600, $[\theta]_{252}$ 0; CD (c 0.1, CH_3OH) $[\theta]_{330}$ 200, $[\theta]_{320}$ 6800, $[\theta]_{310}$ 25,800, $[\theta]_{300}$ 40,800, $[\theta]_{295}$ 42,100, $[\theta]_{290}$ 39,400, $[\theta]_{280}$ 26,200, $[\theta]_{273}$ 17,800, $[\theta]_{272}$ 17,600, $[\theta]_{270}$ 16,300, $[\theta]_{267}$ 11,700, $[\theta]_{265}$ 11,500, $[\theta]_{260}$ 6100, $[\theta]_{258}$ 5500, $[\theta]_{255}$ 3000, $[\theta]_{253}$ 2400, $[\theta]_{247}$ 0.

(−)-(5S)-Isomethadone Hydrochloride (2·HCl, **Figure 4**): CD (c 0.025, $CHCl_3$) $[\theta]_{330}$ −1500, $[\theta]_{320}$ −16,600, $[\theta]_{310}$ −36,800, $[\theta]_{303}$ −45,800, $[\theta]_{300}$ −45,400, $[\theta]_{295}$ −43,200, $[\theta]_{290}$ −36,400, $[\theta]_{280}$ −20,900, $[\theta]_{276}$ −17,300, $[\theta]_{274}$ −15,900, $[\theta]_{270}$ −11,200, $[\theta]_{267}$ −10,500, $[\theta]_{263}$ −5700, $[\theta]_{260}$ −4600, $[\theta]_{257}$ −2800, $[\theta]_{255}$ −2800, $[\theta]_{250}$ −1000; CD (c 0.025, CH_3OH) $[\theta]_{330}$ −1200, $[\theta]_{320}$ −10,800, $[\theta]_{310}$ 24,900, $[\theta]_{303}$ −32,000, $[\theta]_{300}$ −32,100, $[\theta]_{297}$ −32,000, $[\theta]_{290}$ −27,100, $[\theta]_{280}$ −16,300, $[\theta]_{275}$ −12,200, $[\theta]_{273}$ −11,500, $[\theta]_{270}$ −8900, $[\theta]_{267}$ −7700, $[\theta]_{263}$ −4800, $[\theta]_{260}$ −3900, $[\theta]_{258}$ −2600, $[\theta]_{253}$ −1500, $[\theta]_{250}$ −1000.

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Notes

Stereochemical Studies on Medicinal Agents. 17.[1] Synthesis, Absolute Configuration, and Analgetic Potency of Enantiomeric Diastereomers of 3-Ethyl and 3-Propyl Derivatives of 1-Methyl-4-phenyl-4-propionoxypiperidine

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We recently have reported[2] on the relative stereochemistries of racemic diastereomers of 1 and have noted that, unlike the prodines 2, the α isomer is considerably more potent than the β isomer. The corresponding allyl racemates also were found to possess a qualitatively similar stereostructure–activity relationship; however, on a quantitative basis (±)-α-**3** is 15 times more potent than morphine and 24 times that of (±)-α-**1**. A subsequent report[3] on the optical isomers of **3** revealed that α-**3** possesses high enantiomeric stereoselectivity [potency ratio, (3*R*,4*S*)/(3*S*,4*R*) = 260], while the much less active β-**3** exhibits an enantiomeric potency ratio of unity. This is in marked contrast to the stereochemical behavior of α-**2**[4] where potency and enantiomeric stereoselectivity are one order of magnitude lower [(3*R*,4*S*)/(3*S*,4*R*) = 25] than α-*3*. Moreover, β-**2**[4] also shows a striking difference (when compared to β-**3**) in that it possesses moderate enantio-

† This paper is dedicated to Professor Burger in recognition of his many accomplishments in the field of medicinal chemistry.