in 25 ml of liquid NH_3) suspended in 15 ml of PhMe, 1.96 g (0.0084 mole) of 2-chlorophenothiazine was added, the mixture was refluxed for 3 hr, then 1.7 g (0.0084 mole) of XI in 10 ml of PhMe was added, and the whole was refluxed with stirring for 6 hr. After cooling it was extracted with 30 ml of 10% HCl, the aqueous layer was made alkaline with 50% NaOH, and the oil that separated was extracted (Et_2O). The extract was dried (Na_2SO_4), the solvent was evaporated, and the oil residue was treated with dry HCl in ether to give 2.5 g (63%) of II-1·2HCl, mp 189–192° (Et_2O–EtOH).

10,11-Dihydrodibenzocycloheptene Derivatives of 3,8-Diazabicyclo[3.2.1]octanes (III, IV). Synthesis of 8-[5-(10,11-Dihydrodibenzocycloheptenyl)propylidene]-3-methyl-3,8-diazabicyclo[3.2.1]octane (III). (a) Reaction of the Grignard of X with Dibenzosuberone. 8-[5-Hydroxy-5-(10,11-dihydrodibenzocycloheptenylpropyl)] - 3 - methyl - 3,8 - diazabicyclo[3.2.1]octane (XIV).—To a suspension of 0.9 g (0.037 g-atom) of Mg turnings in 10 ml of anhydrous THF, a crystal of I_2 and a few drops of EtBr were added. As the reaction started, a solution of 7.5 g (0.037 mole) of X in 10 ml of THF was added within 0.5 hr. The mixture was refluxed for 1 hr, then 3.9 g (0.085 mole) of dibenzosuberone was added portionwise, and the whole was refluxed for 16 hr. After cooling the resulting solution was dropped into 200 ml of a stirred 10% solution of NH_4Cl at 0°. The oil separated was extracted ($CHCl_3$), the extract was dried, and the solvent was evaporated to give 5.6 g (79%) of XIV, mp 153–155° (Et_2O–petroleum ether). *Anal.* ($C_{25}H_{32}N_2O$) C, H, N.

(b) Dehydration of XIV to 8-[(10,11-Dihydrodibenzocycloheptenyl)propylidene]-3-methyl-3,8-diazabicyclo[3.2.1]octane (III).—A mixture of 5.4 g (0.014 mole) of XIV, 3.3 g (0.017 mole) of *p*-toluenesulfonic acid monohydrate, and 200 ml of PhMe was refluxed 1 hr, then 100 ml of the solvent was slowly distilled. After cooling, the solution was concentrated to a small volume and washed with two 20-ml portions of 10% NaOH. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was chromatographed on silica gel, eluting the impurities with EtOAc–cyclohexane (8:2), then eluting with MeOH to give 4 g (78%) of III as an undistillable oil which exhibited a single spot on tlc.

The **dihydrochloride** melted at 271–273°. *Anal.* ($C_{25}X_{32}Cl_2N_2$) N, Cl.

3-[5-(10,11-Dihydrodibenzocycloheptenyl)propylidene-methyl-3,8-diazabicyclo[3.2.1]octane (IV) was prepared from XI according to the procedure described for III. The intermediate 3-[5-hydroxy-5-(10,11-dihydrodibenzocycloheptenyl)propyl]-8-methyl-3,8-diazabicyclo[3.2.1]octane (XV), mp 167–169° (ether), was isolated in 42% yield. *Anal.* ($C_{25}H_{32}N_2O$) C, H, N.

Dehydration of 2.1 g of XV led to 1.8 g of an oil which was chromatographed on Al_2O_3, eluting with EtOAc–cyclohexane (8:2) to give 1.2 g (60%) of pure IV as undistillable oil.

The dihydrochloride melted at 239–242° ($EtOH$–Et_2O). *Anal.* ($C_{25}H_{32}Cl_2N_2$) N, Cl.

Acknowledgment.—The authors wish to thank Dr. A. Vigevani for spectroscopic determinations and Mr. A. Campi for chemical analyses.

Stereochemical Studies on Medicinal Agents. VII.[1] Absolute Stereochemistry of Methadol Isomers and the Role of the 6-Methyl Group in Analgetic Activity[2,3]

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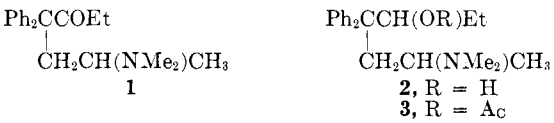
The stereochemistry of optically active α- and β-methadol has been deduced by the asymmetric synthetic procedure of Prelog. The apparent dissociation constants of the title compounds, when compared with those of methadone and 3-deoxymethadone, suggest the absence of substantial intramolecular H bonding in aqueous medium. Nmr and ir studies point to the presence of strong intramolecular H bonds in nonpolar media, with the β isomer being more strongly internally associated. Possible preferred conformations which are consistent with the spectral data are depicted. The (6*R*), (6*S*), and (6*R*) receptor stereoselectivities for methadone, α-methadol, and acetyl-α-methadol, respectively, have been rationalized in terms of differing modes of interaction.

It is generally believed that strong analgetics exert their effect by interacting with specific sites in the CNS, and that these sites possess asymmetric topographies which enable them to distinguish between enantiomorphs.[5]

The more active enantiomers of methadone (**1**) and certain related analgetics possessing a common asymmetric center have been determined to have the (*R*) configuration.[6] It subsequently was pointed out that there are also a number of strong analgetics whose configurations are in the (*S*) series, and that the reversal of stereoselectivity may be due to differing modes of drug–receptor interaction.[7]



1

2, R = H
3, R = Ac

One of the most dramatic and interesting examples of this phenomenon has been in the literature[8,9] for some time and is illustrated in Table I. The more potent α-methadol enantiomer [(−)-α-**2**] is derived from (6*S*)-methadone which has a low order of activity. Moreover, conversion of α-**2** to α-**3** again reverses the stereoselectivity so that the more potent enantiomer, (+)-α-**3**, now has the (6*R*) configuration. With the optically active β isomers there is no inversion of stereoselectivity and, consequently, the activity is found in the (6*R*) series [(−)-β-**2**, (−)-β-**3**].[9]

(1) Part VI of this series: P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968).

(2) We gratefully acknowledge support of this work by National Institutes of Health Grant NB 05192.

(3) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstract P-4. (b) For a preliminary report on this work, see P. S. Portoghese and D. A. Williams, *J. Pharm. Sci.*, **55**, 990 (1966).

(4) NIH Predoctoral Fellow 5-F1-GM-20515, 1963–1966.

(5) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966), and references cited therein.

(6) A. H. Beckett and A. F. Casy, *J. Chem. Soc.*, 900 (1955).

(7) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).

(8) A. Pohland, F. J. Marshall, and T. P. Carney, *J. Am. Chem. Soc.*, **71**, 460 (1949).

(9) N. B. Eddy and E. L. May, *J. Org. Chem.*, **17**, 321 (1952).

TABLE I

ANALGETIC ACTIVITY[a] OF METHADONE, METHADOLS, AND ACETYLMETHADOLS

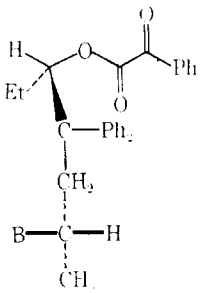
1	ED_{50}, mg/kg	2	ED_{50}, mg/kg	3	ED_{50}, mg/kg
(6*R*)	0.8	(+)-α	24.7	(+)-α	0.3
		(−)-β	7.6	(−)-β	0.4
(6*S*)	25.7	(−)-α	3.5	(−)-α	1.8
		(+)-β	63.7	(+)-β	4.1

[a] Analgetic activities were obtained from ref 9.

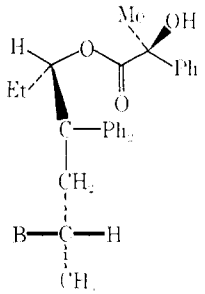
In an effort to explain these remarkable changes in receptor stereoselectivity, an investigation of the complete stereochemistry of the methadol isomers was undertaken.[3] Nmr, ir, and pK_a studies were also carried out in order to investigate the conformational preferences of these molecules.

Chemistry.—Application of Prelog's[10] procedure for determining the absolute configuration of asymmetric carbinols has been employed[11] with great success, and we therefore used this method for our stereochemical studies of the methadol isomers.

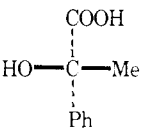
Esterification of (−)-α-methadol with benzoylformyl chloride afforded benzoylformate ester hydrochloride (**4**·HCl) in 95% yield. The free base (**4**), upon reaction



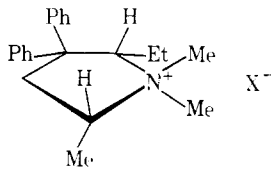
4. B = NMe_2
5. B = $^+NMe_2$ I^-



6. B = NMe_2 or $^+NMe_2$ I^-



7



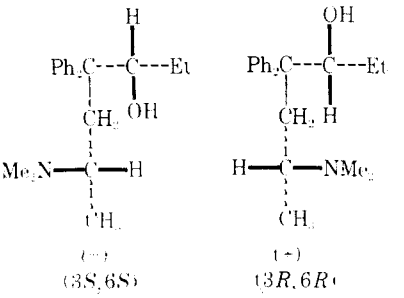
8. X = $PhCOCOO^-$ or Cl^-

with MeMgI, gave rise to the atrolactate ester (**6**, B = NMe_2) which when saponified *in situ*, afforded *S*-(+)-atrolactic acid (**7**) (7.6% optical purity) in an over-all yield of 20% (based on **4**).

The low yield of **7** was likely due to the formation of pyrrolidinium quaternary salt **8** (X = $PhCOCOO^-$) since this compound was isolated when **4** was allowed to stand at room temperature for 3 days. Presumably, this was formed by displacement of the benzoylformyloxy group in **4** *via* intramolecular S_N2 attack by the basic nitrogen. Treatment of **8** (X = $PhCOCOO^-$) with HCl gave the quaternary chloride (**8**, X = Cl^-) which possessed spectral properties identical with the compound isolated by Perrine and May,[12] who had obtained this material in racemic form from reaction of α-methadol with methanesulfonyl chloride. The tentative stereochemistry for **8** was deduced from the configuration of the benzoylformate ester (**4**).

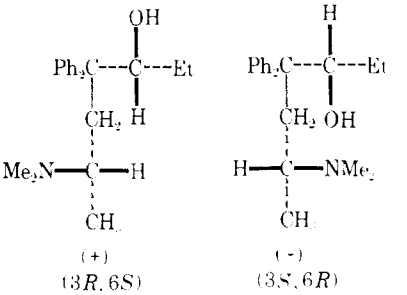
In order to prevent the formation of **8**, the ester (**4**) was quaternized to the methiodide **5** prior to treatment with Grignard reagent. Under these conditions, *S*-(+)-atrolactic acid (optical purity, 7.3%) was obtained in an over-all yield of 81%.

If the diphenylalkyl group, Et, and H are designated large, medium, and small, respectively, and are in the sequence depicted by **4**, then Prelog's rule[10] predicts that approach of Grignard reagent from the less hindered side of the ketonic group should stereoselectively afford the (*S*)-atrolactate ester (**6**). The configuration at C-3 for (−)-α-methadol therefore is assigned to the (*S*) series. Inasmuch as this isomer is derived from (6*S*)-methadone, the complete stereochemistry is designated as (3*S*,6*S*) [(−)-**9**]. Since (+)-β-methadol also is obtained from (6*S*)-methadone, its stereochemistry differs from the (−)-α isomer only at C-3, and hence is assigned the (3*R*,6*S*) configuration [(+)-**10**]. The enantiomers of the preceding methadol isomers, (+)-α- and (−)-β-methadol, therefore, possess the (3*R*,6*R*) [(+)-**9**] and (3*S*,6*R*) [(−)-**10**] stereochemistries, respectively.



(−) (3*S*,6*S*) (+) (3*R*,6*R*)

9



(+) (3*R*,6*S*) (−) (3*S*,6*R*)

10

The configurations of the methadols have been corroborated by pyrolytic cyclization to isomeric 2-ethyl-3,3-diphenyl-5-methylfurans[3b] whose stereochemistries were elucidated by nmr analysis and chemical studies.[13,14]

pK_a Studies.—Dissociation constants have been employed as criteria for assessing the ability of an electronegative group to stabilize the conjugate acid of an amine, as this often gives rise to enhanced basicity due to intramolecular hydrogen bonding.[15] Since

(10) V. Prelog, *Bull. Soc. Chim. France*, 987 (1956).

(11) (a) V. Prelog and H. L. Meier, *Helv. Chim. Acta*, **36**, 320 (1953); (b) W. G. Dauben, D. F. Dickel, O. Jeger, and V. Prelog, *ibid.*, **36**, 325 (1953); (c) A. J. Birch, J. W. Clark-Lewis, and A. V. Robertson, *J. Chem. Soc.*, 3586 (1957).

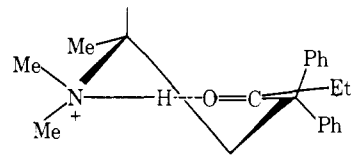
(12) T. D. Perrine and E. L. May, *J. Org. Chem.*, **19**, 773 (1954).

(13) P. S. Portoghese and D. A. Williams, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstracts S-90; P. S. Portoghese and D. A. Williams, *J. Heterocycl. Chem.*, **6**, 307 (1969).

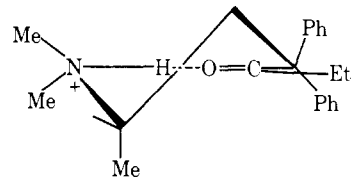
(14) A. F. Casy and M. M. A. Hassan, *Tetrahedron*, **23**, 4075 (1967).

(15) J. F. King in "Technique of Organic Chemistry," Part I, Vol. XI, Interscience Publishers, Inc., New York, N. Y., 1963, Chapter VI, p 318.

methadone and the methadols possess an electronegative group at C-3 which conceivably might stabilize the protonated dimethylamino group, it was of interest to compare the pK_a values of these compounds with 3-deoxymethadone (Table II). The substantially greater basicity of methadone when compared to the deoxy analog suggests that the conjugate acid of methadone assumes a cyclic conformation which is stabilized by internal H bonding.[16] Two possible internally bonded rotamers are depicted by conformations **11a** and **11b**. It is assumed that C=O and the



11a



11b

acidic proton are coplanar so as to allow maximum stabilization. If this is the case, the phenyl groups then would be oriented in "quasi-axial" and "quasi-equatorial" conformations. Accordingly, the C-5 and C-6 substituents would be staggered in "axial" and "equatorial" positions to minimize vicinal nonbonded interactions.

TABLE II
APPARENT DISSOCIATION CONSTANTS FOR METHADONE AND RELATED COMPOUNDS

Compd	pK_a
Methadone	8.62
3-Deoxymethadone	7.93
α-Methadol	7.86
β-Methadol	7.59

The stereospecificity of the catalytic reduction[8,9,17,18] of methadone to α-methadol may be explained in terms of the cyclic conformations. Stuart–Briegleb models indicate the upper face of the carbonyl carbon to be less hindered and hence more accessible to the hydrogenation catalyst. A similar explanation can be invoked to rationalize the stereospecificity of LAH reduction.[18] In this case a cyclic conformation could be maintained by coordination of an aluminum hydride species between N and O functions.

It can be noted (Table II) that the methadol diastereomers are less basic than methadone and its 3-deoxy analog. The decreased dissociation of the methadol diastereomers can be ascribed to one of the following possibilities: (1) there is no substantial intramolecular H bonding of the type, $-(H)O\cdots H-N^+$, or (2) internal $O-H\cdots N$ bonding competes with $-(H)O\cdots H-N^+$ and thereby decreases the stability of the conjugate acid.

Factors contributing to 1 might be related to the lower proton acceptor capacity of the carbinol oxygen (when compared to the carbonyl O of methadone) and to greater steric hindrance to intramolecular association when the H-bonding proton acceptor group is attached to a tetrahedral center. In case 2, $OH\cdots N$ bonding might offset stabilization gained from $-(H)O\cdots H-N^+$ association.

Of the two possibilities, we presently favor **1**.[19] In support of this, existing evidence[20] suggests that $(H)O\cdots H-N^+$ bonds are stronger than $O-H\cdots N$ and hence should substantially increase basicity of tertiary amines by stabilizing the conjugate acid. Since the methadols are less basic than 3-deoxymethadone, it is conceivable that both diastereomers are not internally H bonded in aqueous solution to any great extent. If this is the case, the different pK_a values for α- and β-methadol may be due to differences in accessibility of solvent to stabilize the conjugate acid.

Infrared Studies.—Although evidence suggests that the methadol isomers are not substantially internally H bonded in polar solvents, ir studies indicate the presence of strong intramolecular association in nonpolar media. The high-resolution ir spectra of 0.4 M solutions (CCl_4) of α- and β-methadol bases revealed a broad bonded OH absorption overlapping the CH stretching vibrations at approximately 3000 cm^{-1}.[21] Examination of a 0.005 M solution of the bases showed no change of the absorption characteristics in the 3000-cm^{-1} region. However, some concentration dependence was observed for the α isomer in that a very weak (ϵ 2.5) free OH absorption appeared at 3580 cm^{-1}. No free OH band could be seen with β-methadol. The ir data suggest that both α- and β-methadol are strongly internally H bonded in nonpolar solvent and that the former diastereomer forms weaker H bonds. It has been reported[22] that a chain length of four carbons between electronegative groups gives maximal stability to intramolecular H bonds. The strong internal H bonding observed in the methadol isomers might be due in part to the fact that they possess the optimal number of carbon atoms between the OH and amine functions.

Nmr Studies.—Additional evidence regarding the relative intramolecular H-bonding strengths of α- and β-methadol in nonpolar solvent was obtained by studying the temperature dependence of the hydroxylic proton chemical shift. According to Hyne,[23] the diastereomer which is intramolecularly H-bonded more strongly should show the OH proton resonance as being less temperature dependent. The results of our variable temperature study (Figure 1) show that the regression corresponding to β-methadol has a lower slope than that of the α isomer. The lower temperature

(16) It has been suggested [A. H. Beckett, *J. Pharm. Pharmacol.*, **8**, 848 (1956)] that intramolecular association of this type could occur with methadone, although it was found that 3,3-diphenyl-N,N-dimethylpropylamine is a stronger base than 6-desmethylmethadone. A possible explanation for these results might be related to the fact that the former is not a good model compound, since it does not possess a substituent comparable to the size of the propionyl group.

(17) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(18) M. E. Speeter, W. M. Byrd, L. C. Cheney, and S. B. Binkley, *J. Am. Chem. Soc.*, **71**, 57 (1949).

(19) In our preliminary report[4b] we suggested the presence of $(H)O\cdot H-N^+$ bonding. Subsequently, however, the apparent pK_a value determined for 3-deoxymethadone indicated this to be no longer tenable.

(20) H. Rapaport and S. Masamune, *J. Am. Chem. Soc.*, **77**, 4330 (1955).

(21) A similar observation was reported [A. M. DeRoos and G. A. Bakker, *Rec. Trav. Chim.*, **81**, 219 (1962)] with several hydroxypropylamines.

(22) A. B. Foster, A. H. Haines, and M. Stacey, *Tetrahedron*, **16**, 177 (1961).

(23) J. B. Hyne, *Can. J. Chem.*, **38**, 125 (1960).

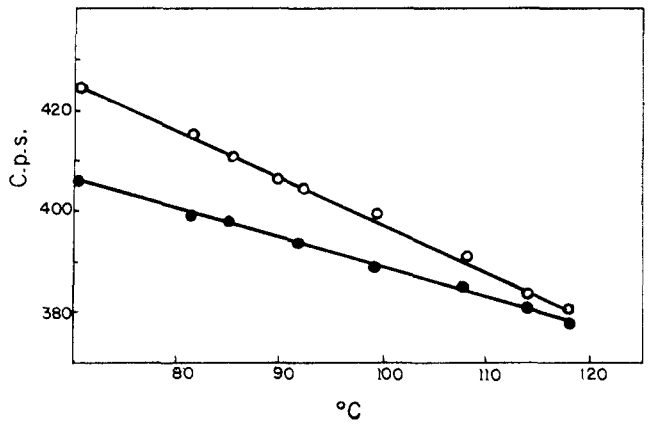
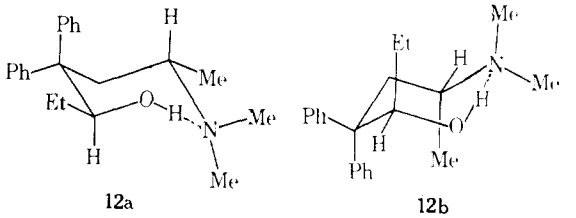


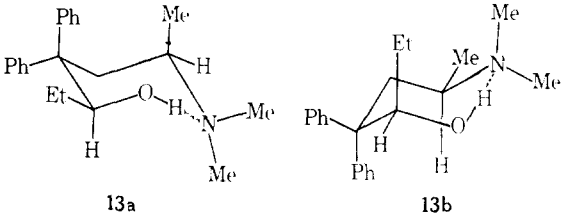
Figure 1.—The temperature dependence of the *OH* resonance for α-methadol (○) and β-methadol (●) in C_2Cl_4.

dependence for the OH resonance of β-methadol suggests that it is more strongly H bonded.

The qualitative difference in H-bond strength can be rationalized in terms of "chair-like" conformations **12** and **13** for α- and β-methadol, respectively. If "diaxial" Ph–Me interactions are important in destabilizing **12b** and **13a**, then **12a** and **13b** should be the primary contributors to the rotameric populations. Stuart–Briegleb models reveal that **13b** is less hindered than **12a**, since the *gauche* interaction between the two phenyl rings and the ethyl group in the latter is considerably greater than the single *gauche* interaction between these groups in the former. It might be expected that a


12a

12b


13a

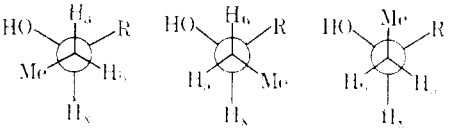
13b

double *gauche* interaction would not simply be double that of a single interaction, but greater, since one phenyl group should influence the orientation of the second. Molecular models also indicate that a "diaxial" interaction between the Et and the C-5 proton in **13b** probably is much less than that found in cyclohexane because of the flexibility of the molecule.

Hence, the more stable "chair-like" conformation of β-methadol (**13b**) should be less hindered than that of α-methadol (**12a**), and this is consistent with the results obtained from the proton-exchange studies which indicated the β isomer to be more strongly intramolecularly H bonded.

In $CDCl_3$, the OH protons of α- and β-methadol are seen at 8.3 (W_H = 30 cps) and 7.9 (W_H = 23 cps) ppm, respectively. The appearance of OH absorption at unusually low field suggests the presence of strong H bonds.[24] At −40°, the proton in β-methadol exhibited a doublet (J = 10 cps) at 8.5 ppm, whereas the α isomer showed a singlet at 9.7 ppm (W_H = 10 cps). The large coupling constant observed for the β isomer is suggestive of *trans* coupling[25] and is consistent with conformation **13b**. The presence of the broad singlet for α-methadol suggests that the OH exchange rate at −40° is too rapid for coupling to be observed. Since *gauche* CH–OH coupling has been found[25] to be between 2 and 3 cps, it is likely that coupling would be observed at lower temperature.[26]

Another feature of the nmr spectra of α- and β-methadol which was unobscured by other proton resonances was the carbinol proton absorption. The features of these resonances were of interest because they might possibly provide information on the dihedral relationship between the C-2 CH_3 protons and the carbinol proton. The carbinol proton would be expected to display a pattern characteristic of an X proton in an ABX spin system. The carbinol proton resonance for α-methadol base ($CDCl_3$) was seen as a quartet (J = 10 and 3 cps) centered at 3.87 ppm and is characteristic of *trans* and *gauche* vicinal coupling. Projection formulas **14a**, **14b**, and **14c** illustrate the possible staggered conformations for the C-2,3 centers in these diastereomers. The coupling is consistent either with **14a** or **14b** as the predominant rotamers. Of these two possibilities, it would be expected that **14a** would be favored since the remainder of the molecule is 180° removed from CH_3.


14a 14b 14c

The β isomer shows an unresolved resonance (W_H = 13 cps) at 4.0 ppm for the carbinol proton. Since this diastereomer has been determined to be more strongly intramolecularly H bonded than the α isomer, it was thought that the OH proton exchange rate might be sufficiently reduced to permit coupling with the carbinol proton and that this might be the reason for the observed multiplicity. Indeed, the resonance resolved itself into an ill-defined quartet (J = 8 and 4 cps) on treatment with D_2O. However, the broadness of the peaks suggested that factors other than coupling with OH were responsible for this phenomenon. Interestingly, there was no observable change when α-methadol was exchanged with D_2O, which is consistent with our findings that this diastereomer is less strongly internally H bonded than the β isomer.

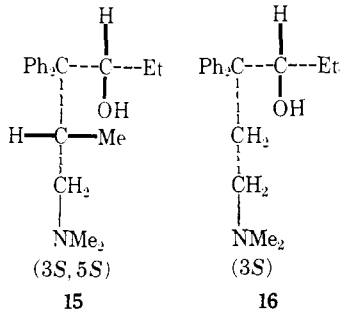
Stereostructure–Activity Relationship.—The more active enantiomers of α- and β-methadol [(−)-**9** and (−)-**10**, respectively] have in common the (3*S*) configuration. Since the stereochemistry at C-6 in these isomers is (*S*) and (*R*), respectively, it appears that the OH group is of importance in orienting the molecule at the receptor surface, with the 6-Me playing a relatively

(24) G. C. Pimentel and A. L. McCellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, p 145.

(25) E. F. Kiefer, W. Gericke, and S. T. Amimoto, *J. Am. Chem. Soc.*, **90**, 6246 (1968).

(26) We were unable to study α-methadol at temperatures below −40° due to crystallization of the solute.

minor role. This is consistent with the stereochemistry of the active isomethadol antipode (**15**)[27] which also possesses the (3*S*) configuration.[28] Moreover, it recently has been reported that the configuration of the more active enantiomer of normethadol (**16**) also is (3*S*).[29]



It has been suggested previously that the constitution and geometric disposition of an H-bonding group on the analgetic molecule has an important bearing on the antipodal discriminatory power of analgetic receptors.[7,30] If the reasonable assumption is made that there are several donor and acceptor H-bonding dipoles situated in different locations on the receptor, the varying stereoselectivities of the analgetic–receptor interaction can be rationalized on this basis. According to this concept,[7] the steric course of the drug–receptor interaction would depend upon the particular receptor dipole involved in H bonding, and this would be a function of the constitution of the H bonding group of the analgetic and also upon the over-all conformation of the molecule. This is illustrated schematically in Figure 2. The great difference in C-6 stereoselectivity between methadone and α-methadol could arise from the possibility of the carbonyl oxygen of methadone acting as a proton acceptor (Figure 2A) and the OH behaving as a proton donor (Figure 2B). This would lead to different modes of interaction of these molecules with analgetic receptors with the result that the C-6 asymmetric centers would be located in different steric environments. In this regard, it appears that the receptor environment in the vicinity of the C-6 center of the more active enantiomers of α- and β-methadol does not have high steric demands, since the configurations of the more active enantiomers are (6*S*) and (6*R*), respectively. However, with methadone, the mode of binding is such that the configuration at the C-6 asymmetric center is important.

When α-methadol is acetylated, the receptor stereoselectivity changes from (6*S*) to (6*R*) (Table I). This possibly could be related to the fact that such a conversion eliminates the H-bonding donating potential of the C-3 group. Thus, the C-3 function can now act only as a proton acceptor, and this alters the mode of interaction (Figure 2C). Since the more active enantiomers of both α- and β-methadol acetates possess opposite configurations at C-3, this asymmetric center no longer appears to be of primary importance. This suggests that the steric environment of the receptor in proximity with the C-3 center of the acetate esters is essentially

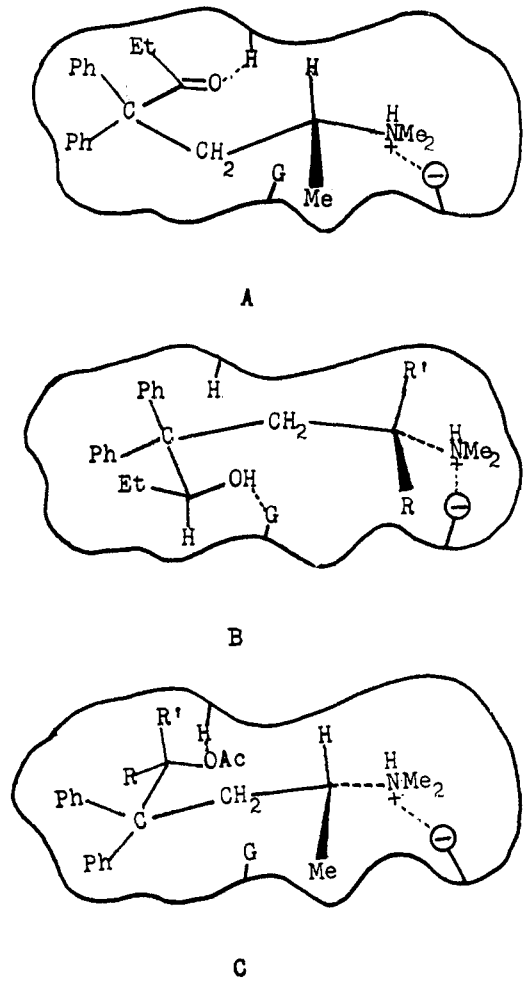


Figure 2.—A schematic illustration rationalizing changes in the C-6 and C-3 stereoselectivities of analgetic receptors. Hydrogen-bonding proton donor (H) and acceptor (G) dipoles located in different positions on the receptor are believed to play an important role in the orientation of the analgetic molecule. (−)-α-**2** (R = H, R′ = Me) and (−)-β-**2** (R = Me, R′ = H) are represented in illustration B. (+)-α-**3** (R = H, R′ = Et) and (−)-β-**3** (R = Et, R′ = H) are shown in C.

different and less demanding than the highly stereoselective force field interacting with C-3 of the more active methadol isomers.

Although we have illustrated only one proton donor and one proton acceptor dipole on the receptor, there may be more than one of each type. For instance, it is conceivable that the C-3 proton acceptor function of two analgetics may be involved in H bonding with different proton donor dipoles located on the receptors. This would also result in a change in the mode of binding. Examples of this type may occur with methadone, its carbethoxy analog, and the basic anilides. All of these analgetics possess a C=O; however, their modes of interaction have been analyzed as being different from one another.[5,7]

It should be emphasized that all of the changes in stereoselectivity may also be rationalized on the basis of there being more than one receptor species for analgetic activity.[5,7] Two receptor species, α and β, may have different steric demands due to differences in the locations of H-bonding dipoles. If analgetic A were bound preferentially by α receptors and B by β receptors, then a difference in stereoselectivity also would be observed.

(27) E. L. May and N. B. Eddy, *J. Org. Chem.*, **17**, 1210 (1952).
(28) P. S. Portoghese and D. A. Williams, *Tetrahedron Letters*, 6299 (1966).
(29) A. F. Casy and M. M. A. Hassan, *J. Med. Chem.*, **11**, 601 (1968).
(30) P. S. Portoghese and D. L. Larson, *J. Pharm. Sci.*, **53**, 302 (1964).

Experimental Section[31]

(−)-α-Methadol Benzoylformate Hydrochloride (4·HCl).—An EtOAc solution (7 ml) containing 0.531 g (0.0017 mole) of (−)-α-methadol and 0.46 g (0.0027 mole) of benzoylformyl chloride was refluxed for 6 hr. After cooling in an ice bath, the product (0.55 g) was filtered and recrystallized (EtOH–EtOAc); yield 0.5 g (61%), mp 195–196° dec, $[\alpha]^{24}D$ −67.3° (*c* 1.25, MeOH). Absorption bands (ir) were as expected. A portion of this was converted to the chloroplatinate salt, mp 201–202°. *Anal.* [2($C_{29}H_{33}NO_3$)·H_2PtCl_6]C, H, N.

(−)-α-Methadol Benzoylformate Methiodide (5).—A suspension of 0.5 g (0.001 mole) of finely powdered **4**·HCl in 20 ml of chilled EtOAc–Me_2CO (1:1) was treated with an equivalent amount of freshly prepared Ag_2O and shaken vigorously for 10 min with intermittent cooling. The addition of excess MeI to the filtered solution and cooling overnight yielded 0.44 g (70%) of product, mp 208–210° dec, $[\alpha]^{24}D$ −42.8° (*c* 1, MeOH) after recrystallization (MeOH). *Anal.* ($C_{30}H_{36}INO_3$) C, H, N.

Reaction of (−)-α-Methadol Benzoylformate Methiodide with Methylmagnesium Iodide.—A tenfold excess of MeMgI and 0.4 g (0.0068 mole) of finely powdered **5** was stirred under N_2 for 3 hr. The reaction mixture was decomposed with cold, saturated NH_4Cl and the solvent was removed *in vacuo*. MeCN was added to the solid residue, and the insoluble inorganic salts were filtered. Removal of solvent afforded a brown oil, which was refluxed with 5% MeOH–KOH for 6 hr. The MeOH was removed and H_2O was added to the residue which then was extracted with EtOAc. The alkaline extract was acidified (HCl), extracted several times with EtOAc, and dried, and the solvent was removed *in vacuo*. The resultant oil was extracted several times with $NaHCO_3$ solution, acidified (HCl), extracted (EtOAc), and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield 0.093 g (82%) of (+)-atrolactic acid. Recrystallization from cyclohexane afforded pure atrolactic acid, mp 89–91°, $[\alpha]^{24}D$ +4.15° (*c* 1, 1 *N* NaOH), corresponding to 7.3% optical purity.[32]

Reaction of (−)-α-Methadol Benzoylformate with Methylmagnesium Iodide.—A suspension of 0.8 g (0.0917 mole) of **4**·HCl in H_2O was shaken with NH_4OH, the free base was extracted into Et_2O and dried, and the solvent was removed *in vacuo*. After drying *in vacuo*, the residue was dissolved in dry PhH (10 ml) and added dropwise to a fourfold excess of MeMgI in Et_2O. The solution was stirred for 1 hr and then refluxed for 1 hr. The mixture was decomposed with saturated NH_4Cl, extracted several times (Et_2O), and dried and the solvent was removed *in vacuo*. The resultant oil was saponified by refluxing in 10% MeOH–KOH for 4 hr. The cooled solution was diluted (H_2O) and extracted (Et_2O). The aqueous layer was acidified with HCl, extracted (Et_2O), and dried. Removal of solvent *in vacuo* and addition of petroleum ether (bp 60–68°) afforded crude atrolactic acid which, after treatment with activated charcoal, afforded 0.05 g (20%) atrolactic acid, mp 86–87°, $[\alpha]^{24}D$ +4.1° (*c* 1, 1 *N* NaOH).

(+)-1,1,5-Trimethyl-2-ethyl-3,3-diphenylpyrrolidinium Benzoylformate.—A suspension of 2.1 g (0.0044 mole) of **4**·HCl in H_2O was shaken with dilute NH_4OH followed by extraction (Et_2O), dried, then concentrated *in vacuo*. The resultant oil was dried *in vacuo* for 3 days, and, upon addition of dry benzene, 0.5 g (24%) of a yellow solid, mp 209–210° dec, was obtained. This product was recrystallized (EtOH–Et_2O), mp 211–213° dec, $[\alpha]^{24}D$ +98.3° (*c* 0.93, MeOH). Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{29}H_{33}NO_3$) C, H, N.

(+)-1,1,5-Trimethyl-2-ethyl-3,3-diphenylpyrrolidinium Chloride.—An EtOH solution of **8** (benzoylformate) was acidified to a congo red end point with HCl and evaporated to dryness. The resultant solid was crystallized from EtOAc to give the chloride salt, mp 264–265° dec, $[\alpha]^{24}D$ +129.1° (*c* 0.95, MeOH). The ir spectrum was virtually identical with racemic material provided by May.[32]

Apparent Dissociation Constants.—Approximately 0.02 *M* of the HCl salts were dissolved in analytical grade MeOH (5 ml) and titrated against aqueous 0.115 *N* NaOH. The titration curves were recorded using a Radiometer automatic titrator Model TTT-1, outfitted with an autoburette and recorder (Radiometer-Copenhagen, the London Co., Westlake, Ohio). The titrations were carried out at 23° under constant conditions and the average values of three determinations are recorded in Table II.

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(31) All melting points were recorded using a Thomas–Hoover melting point apparatus and are corrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Routine ir spectra were recorded using a Perkin-Elmer 237B spectrophotometer, and high-resolution ir spectra were obtained on a Perkin-Elmer 521 spectrophotometer. Nmr spectra were recorded using a Varian A-60 spectrometer, (TMS) at ambient temperature of the magnet, and under variable temperature conditions the temperature was monitored using a Honeywell potentiometer Model No. 2705. Optical rotations were obtained using a Perkin-Elmer 114 polarimeter with a 1-dm cell.

(32) A. Mckenzie and C. Clough, *J. Chem. Soc.*, **97**, 1016 (1910).