(13) M. H. Akhtar, A. Begleiter, D. Johnson, J. W. Lown, L. McLaughlin, and S. K. Sim, *Can. J. Chem.*, **53**, 2891 (1975).
(14) D. P. Rall and C. G. Zubrod, *Annu. Rev. Pharmacol.*, **2**, 109 (1962).
(15) J. S. Driscoll and R. Geran, unpublished results.
(16) A. H. Khan and J. S. Driscoll, *J. Med. Chem.*, **19**, 313 (1976).
(17) K. T. Finley in "Chemistry of Quinonoid Compounds, Part 2", S. Patai, Ed., Wiley, New York, N.Y., 1974, p 1101.
(18) Farbenfabriken Bayer A.-G., British Patent 762 723 (Dec 5, 1956).
(19) Farbenfabriken Bayer A.-G, British Patent 793 796 (April 23, 1958).
(20) A. Marxer, *Helv. Chim. Acta*, **40**, 502 (1957).
(21) Farbenfabriken Bayer A.-G., German Patent 943 166 (August 16, 1956).
(22) A. Marxer, U.S. Patent 2 802 001 (August 6, 1957).
(23) S. Petersen, W. Gauss, and G. Domagk, U.S. Patent 2 913 453 (Nov 17, 1959).
(24) A. Marxer, U.S. Patent 3 040 030 (June 19, 1962).
(25) K. Wallenfals and W. Draber, *Angew. Chem.*, **70**, 313 (1958).
(26) K. Wallenfals and W. Draber, *Justus Liebigs Ann.* Chem., **667**, 55 (1963).
(27) A. N. Makarova, V. S. Martynov, and A. Ya. Berlin, *Zh. Obshch. Khim.*, **33**, 1643 (1963).
(28) C. Hansch, *Cancer Chemother. Rep.*, **56**, 433 (1972).
(29) B. F. Cain, *Cancer Chemother. Rep.*, **59**, 679 (1975).
(30) H. Wagner and H. Berg, *J. Electroanal. Chem.*, **2**, 452 (1961).
(31) P. Zuman, *Collect. Czech. Chem. Commun.*, **27**, 2035 (1962).
(32) P. Zuman, "Substituent Effects in Organic Polarography", Plenum Press, New York, N.Y., 1967.
(33) See J. Q. Chambers in ref 17, p 737.
(34) W. C. J. Ross, "Biological Alkylating Agents", Butterworths, London, 1962.
(35) S. Kinoshita, K. Uzu, K. Nakano, and T. Takahashi, *J. Med. Chem.*, **14**, 109 (1971).
(36) C. Hansch and A. Leo, Pomona College Medicinal Chemistry Project.
(37) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
(38) R. W. Taft in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956.
(39) V. S. Martynov, A. N. Makarova, and A. Ya. Berlin, *Zh. Obshch. Khim.*, **34**, 2807 (1964).
(40) J. A. Beisler (NCI) and J. V. Silverton (NHLI), unpublished data.
(41) K. D. McMurtrey and G. D. Davis, *J. Org. Chem.*, **35**, 4252 (1970).
(42) J. Mattern, K. Wayss, and M. Volm, *Arch.* Gynaekol., **216**, 273 (1974).
(43) J. Hartleib, *Z. Krebsforsch.*, **81**, 1 (1974).
(44) H. Nakao and M. Arakawa, *Chem. Pharm. Bull.*, **20**, 1962 (1972).
(45) H. Nakao, M. Arakawa, T. Nakamura, and M. Fukushima, *Chem. Pharm. Bull.*, **20**, 1968 (1972).
(46) T. Saito, S. Ohira, A. Wakui, M. Yokoyama, et al., *Cancer Chemother. Rep.*, **57**, 447 (1973).
(47) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3** (2), 1 (1972).
(48) R. I. Geran, G. F. Congleton, L. E. Dudeck, B. J. Abbott, and J. L. Gargus, *Cancer Chemother. Rep., Part 2*, **4** (4), 53 (1974).
(49) P. C. Merker, I. Wodinsky, and R. I. Geran, *Cancer Chemother. Rep.*, **59**, 729 (1975).
(50) A. J. Repta, B. J. Rawson, R. D. Shaffer, K. B. Sloan, N. Bodor, and T. Higuchi, *J. Pharm. Sci.*, **64**, 392 (1975).
(51) J. Epstein, R. W. Rosenthal, and R. J. Ess, *Anal. Chem.*, **27**, 1435 (1955).
(52) A. J. Lin and A. C. Sortorelli, *Biochem. Pharmacol.*, **25**, 206 (1976).

Stereochemical Studies on Medicinal Agents. 21.[1] Investigation of the Role of Conformational Factors in the Action of Diphenylpropylamines. Synthesis and Analgetic Potency of 5-Methylmethadone Diastereomers

James G. Henkel, Eric P. Berg, and Philip S. Portoghese*

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455.
Received April 1, 1976

The synthesis of racemic *threo*- and *erythro*-5-methylmethadone (**3a** and **3b**, respectively) was carried out and the solution conformation of each isomer was investigated through pK_a and NMR studies. The data indicate that **3a**·HCl exists exclusively in an internally hydrogen-bonded conformation while the erythro isomer **3b**·HCl is present as a mixture of conformations. The erythro racemate **3b** was found to possess 5.4 times the analgetic potency of (±)-methadone in contrast to the threo racemate **3a** which was inactive and devoid of antagonist activity. The fact that the inactive racemate **3a** contains the 5*S*,6*R* stereoisomer, which combines the configurations found in the more active enantiomers of methadone and isomethadone, suggests that the chiral centers do not behave as independent units and that conformational factors are playing an important role in governing stereoselectivity. These results, when analyzed together with earlier reports, suggest that one of the pharmacophoric conformations of the diphenylpropylamine analgetics possesses an antiperiplanar-like disposition of the Ph_2CCOEt and $^+NHMe_2$ groups.

One of the most widely studied classes of synthetic analgetics has been the diphenylpropylamines,[2] of which methadone (**1**) and isomethadone (**2**) have played a central role. Many compounds in this group have chiral centers in common with either **1** or **2**, and numerous investigations pertaining to the steric requirements for analgetic activity have been reported.[3-5]

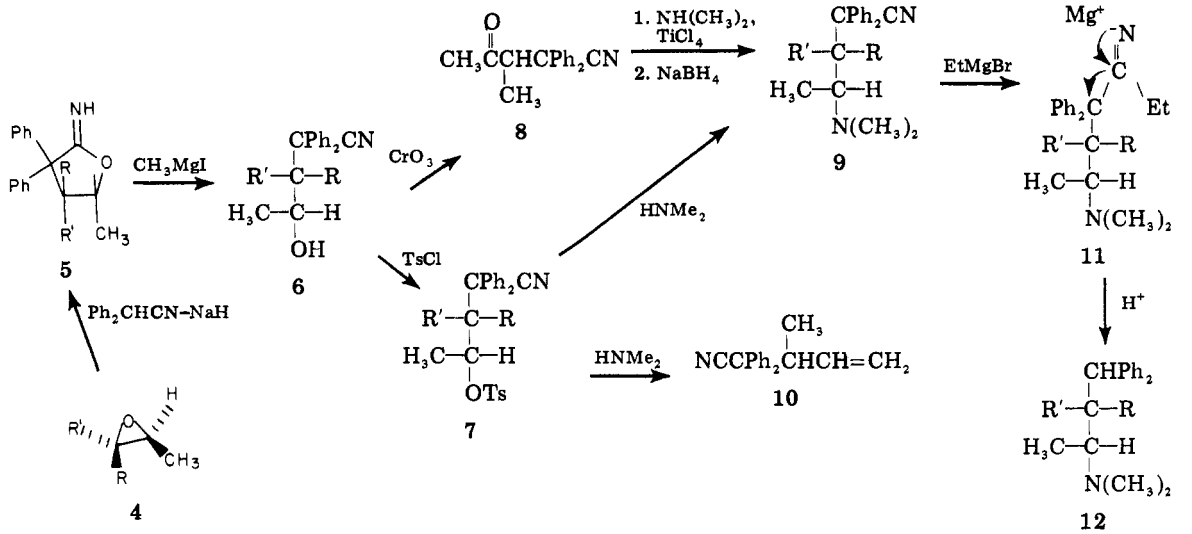
$CH_3CH_2COCPh_2CHRCHR'NMe_2$

1, R = H; R' = CH_3
2, R = CH_3; R' = H

One aspect of the structure–activity relationship which has been the subject of recent inquiry is the fact that some methadone-related compounds show inversion of antipodal stereoselectivity at analgetic receptors.[6] As no such inversions occur with analgetics related to **2**, it was suggested that this could be due in part to the greater conformational flexibility of **1** relative to **2**.[7] This was later given additional support by the finding that a solution of **1** consists of comparable fractions of three gauche conformers while **2** exists predominantly as the chain-extended rotamer (either as the bases or the salts).[8] However, because of the conformational heterogeneity of methadone, no correlation between conformation and activity of **1** and **2** was made.

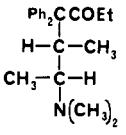
In an effort to provide further insight into the stereostructure–activity relationship of the diphenylpropylamines and analgetic potency, we have synthesized

Scheme I

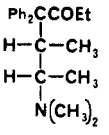


a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

and tested two diastereomeric racemates of 5-methylmethadone (**3a,b**). The rationale for preparing **3a** and **3b** was based on the expectation that there would be a substantial difference in their conformational preference and that this would be reflected by a large potency difference. The results of the present study indicate this to be the case and suggest that an antiperiplanar-type orientation between NMe_2 and CPh_2COEt favors analgetic activity.



3a



3b

Chemistry. Initially, the approach to the stereospecific synthesis of each of the diastereomers **3a** and **3b** was similar to Easton's[9] synthesis of methadone (Scheme I). Stereospecific opening of the *cis*- and *trans*-2-butene oxides (**4**) with diphenylacetonitrile anion afforded *trans*- and cis-iminotetrahydrofurans **5a** and **5b**, respectively. Treatment of **5** with MeMgI produced the corresponding *threo*- and *erythro*-2,2-diphenyl-3-methyl-4-hydroxyvaleronitriles **6a** and **6b**. Reaction of **6** with *p*-toluenesulfonyl chloride gave the corresponding tosylate esters **7a** and **7b**. Conversion of **7a** to the corresponding *erythro*-aminonitrile **9b** with dimethylamine was attempted under a variety of conditions. In every case, high yields of olefin **10** were isolated along with small amounts of **9b**. Efforts to circumvent this elimination reaction during the nucleophilic displacement were unsuccessful, and as it became clear that this approach was not feasible, an alternative scheme was developed. This route involved the oxidation of **6** to ketonitrile **8**, with the concomitant loss of one of the chiral centers. Despite this disadvantage, the ready availability of **6a** and **6b** made it an attractive alternative.

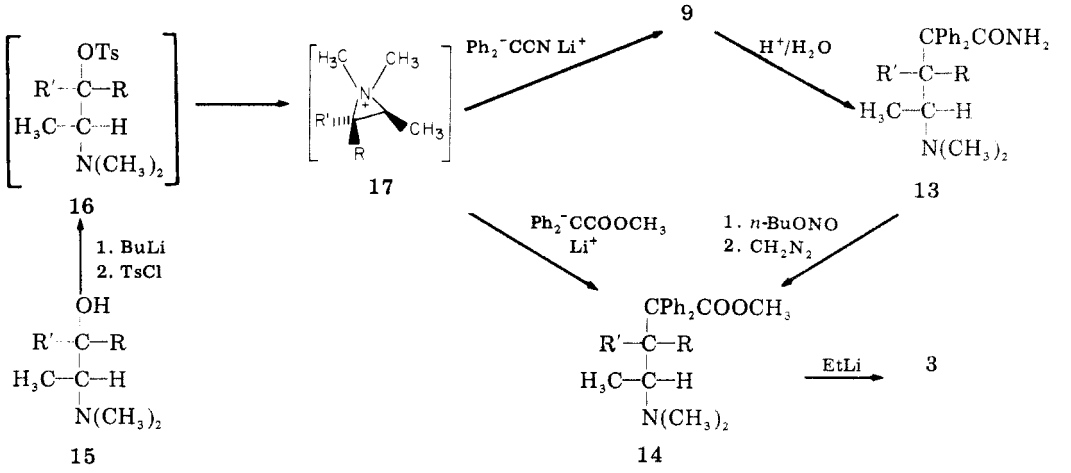
Starting from *threo*-hydroxynitrile **6a**, oxidation with CrO_3–pyridine[10] afforded **8** in good yield. Reductive amination of **8** with $NaBH_3CN$[11] was not successful despite repeated attempts under varying conditions. Amination finally was accomplished using dimethylamine and $TiCl_4$,[12] followed by reduction catalytically or with sodium borohydride. Interestingly, the only product which was formed was found to be identical with the minor product **9b** resulting from the reaction of dimethylamine with **7a**.

It was decided that the feasibility of the conversion of **9b** to **3b** should be investigated before more effort was spent on the threo system. Thus, when **9b** was treated with ethylmagnesium bromide in refluxing toluene[13,14] or at 20 °C, either unreacted starting material was recovered or decyanated product **12b** was formed, presumably as a consequence of thermal decomposition of intermediate **11b**. Although cleavage has not been reported in the case of **1** or **2** under these conditions, similar behavior has been reported in the presence of sodium amide.[15] The cleavage reaction also was observed when **9b** was treated with ethyllithium at lower temperature.

In view of these unexpected results, an alternative four-step method for the conversion of **9b** to **3b** was used, which makes use of ester **14b**. It was believed that the difficulties experienced with dimethylaminonitrile **9** could be circumvented by the addition of ethyllithium to **14**, as this would produce an intermediate which would eliminate the less basic methoxide group upon hydrolysis, rather than the diphenylalkane group. In an effort to produce the desired intermediate **14b**, the acid hydrolysis of **9b** was undertaken. This hydrolysis proceeded only as far as amide **13b**. The conversion of **13b** to **14b** was accomplished with *n*-butyl nitrite[16] followed by treatment with diazomethane. With **14b** in hand, its conversion to **3b** by the action of ethyllithium proceeded in excellent yield.

In view of the availability of only a small amount of **3b** and the likelihood that preparation of **3a** would be troublesome due to the fact that the isomer **9a** was not obtainable by this route, an alternate stereospecific synthesis of **3** was devised. Since the introduction of the dimethylamino group was the source of considerable difficulty, an approach was chosen which placed it into the molecule at an earlier point (Scheme II). The relative stereochemistry of the products also was assured by the presumed anchimeric participation of the dimethylamino group during the key alkylation step proceeding through **17**. This route proved to be successful for both stereoisomers, although differences in chemical reactivities of the two systems necessitated some modifications. The starting material for each isomer was *threo*- and *erythro*-3-dimethylamino-2-butanol (**15a** and **15b**, respectively), obtained from **4a** and **4b** by a modification of the method of Smissman et al.[17] For the synthesis of the threo isomer **3a**, **15a** was treated with 1 equiv of *p*-toluenesulfonyl

Scheme II



a, R = CH_3; R' = H
b, R = H; R' = CH_3

Table I. Vicinal Coupling Constants $J_{5,6}$ for 5-Methylmethadone Diastereomers 3a,b and Their HCl Salts[a]

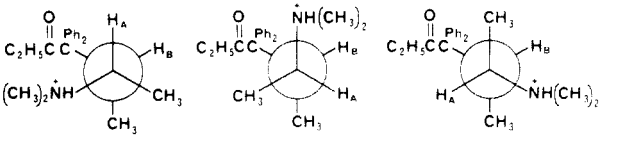
Compd	Hz ($CDCl_3$)	Hz (CD_3OD)	Hz (D_2O)
(±)-3a	6.7	7.0	b
(±)-3b	7.2	7.6	b
(±)-3a·DCl	≲1[c]	b	≲1[c]
(±)-3b·DCl	8.3	6.6	6.0

[a] Determined at 100 MHz with decoupling unless noted otherwise. [b] Not determined. [c] Determined at 270 MHz with decoupling.

chloride to afford the highly reactive ester **16a**, which was converted in situ to **14a** with excess $Ph_2C^-COOMe\ Li^+$. Conversion of **14a** to **3a** was accomplished by the addition of ethyllithium, as described earlier.

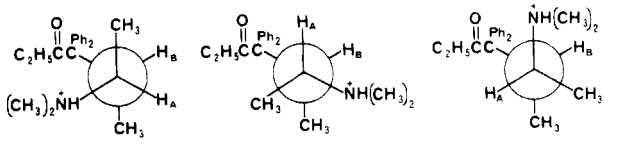
The other diastereomer **3b** also was synthesized by the above route. However, in the case of **16b**, addition of $Ph_2C^-COOMe\ Li^+$ resulted in a low (<10%) yield of **14b**, thus necessitating a modification of the alkylation step. To reduce what was felt to be a higher degree of steric hinderance about the alkylation site due to the trans disposition of the two methyl groups, diphenylacetonitrile anion was employed for the alkylation of **16b**, affording a 60% yield of **9b**. Conversion of **9b** to **3b** was then carried out as described earlier. The stereospecificity of this scheme also was demonstrated by the conversion of **15a** to **9a**.

NMR Studies. In an effort to gain some insight into the conformational flexibility and rotamer distribution of **3a** and **3b**, the high-resolution NMR spectra of both the free bases and the HCl salts were determined in $CDCl_3$, CD_3OD, and (for the salts) D_2O. Of special interest was the magnitude of the C-5,6 vicinal coupling constant, which is known to be sensitive to solvent polarity changes in the methadone system but relatively insensitive in the case of isomethadone.[8] The magnitudes of $J_{5,6}$ for both systems in various solvents are shown in Table I. With the free bases, the coupling constants seem to reflect a nearly equal distribution of the rotameric population about the C-5,6 bond. Perhaps more significantly, the corresponding DCl salts of **3a** and **3b** exhibit widely divergent C-5,6 coupling constants. This is likely a reflection of extreme differences in the respective conformational populations. The coupling constant for erythro racemate **3b**·DCl in $CDCl_3$ suggests a somewhat unequal distribution of rotamers **18a–c**. Increasing the solvent polarity brings the coupling into the range which usually is indicative of a population that is equally divided. These data suggest that **3b**·DCl is quite flexible and that the barriers for conformational interconversion are not inordinately high. Of course, it should be noted that the behavior of **3b**·HCl may well be rationalized in terms of off-staggered conformers and that the truly staggered conformations presented here are serving only as a reasonable first approximation to the actual distribution.



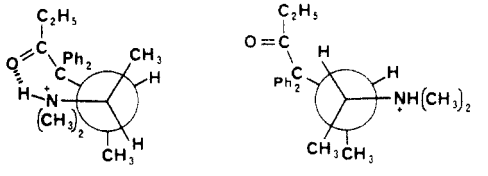
18a **18b** **18c**

In contrast to its diastereomer, the threo salt (**3a**·DCl) exhibits a uniformly small coupling constant (≤1 Hz) in solvents of widely different polarity. The magnitude of the observed coupling constant effectively rules out contribution by all three staggered rotamers (**19a–c**) because the contribution of **19a** and **19b** would be expected to produce an observed coupling constant in the order of



19a **19b** **19c**

2.5 Hz, while $J_{5,6}$ for **19c** should be at least 12 Hz.[18] A plausible explanation for the small coupling constant is that **3a**·DCl exists almost exclusively as an off-staggered conformation, resulting in near orthogonality of methine protons H_a and H_b as shown in **20a**. The alternative rotamer of **3a**·DCl containing orthogonal protons, **20b**, is not expected to contribute, due to both a lack of internal H-bonded stabilization (see pK_a Studies) and the presence



20a **20b**

of severe nonbonded interaction due to partial eclipsing

Table II. Dissociation Constants of 5-Methylmethadone Hydrochloride Diastereomers in Methanol-Water[a]

Compd	pK_a
(±)-3a·HCl	8.71
(±)-3b·HCl	8.16
Methadone HCl (1·HCl)	8.62[b]
Isomethadone HCl (2·HCl)	7.76[c]

[a] Determined in MeOH-H_2O by the method described in ref 6. [b] See ref 6. [c] See ref 7.

Table III. Analgetic Potencies of Racemic 5-Methylmethadone Diastereomers

Compd	ED_{50}, mg/kg[a]	Rel potency
(±)-3a·HCl	>50	Inactive
(±)-3b·HCl	0.36 ± 0.08	5.4
(±)-1·HCl	1.95 ± 0.40[b]	1

[a] Administered sc as solution in normal saline. [b] Lit.[2] 1.62 mg/kg.

of the vicinal methyl groups. While a difference in the observed coupling constants for the DCl salts is understandable when viewed on the basis of the above arguments, the insensitivity of $J_{5,6}$ to changes in solvent polarity is somewhat surprising and may be indicative of an unexpectedly high stabilization due to strong intramolecular hydrogen bonding.

pK_a Studies. In an effort to further elucidate the solution conformational populations of the salts of **3a** and **3b**, their apparent dissociation constants were determined. The results are shown in Table II, along with values for methadone and isomethadone. The threo isomer proved to be more basic than the erythro isomer by 0.55 pK_a units. Since it is unlikely that this is due to differences in the electronic states of the closely related isomers, it is probable that the greater basicity of **3a** is a consequence of stronger internal hydrogen bonding of the respective conjugate acid.[6,7,19] Moreover, it appears that hydrogen bonding is greatly facilitated by conformational factors; this is consistent with the conclusions drawn from the preceding NMR studies.

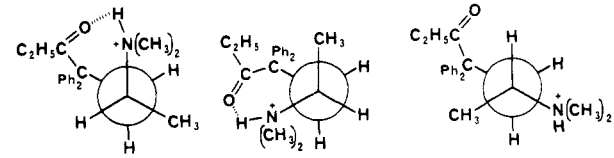
Pharmacology. The analgetic potencies of **3a**·HCl and **3b**·HCl (Table III) were determined 15 min after sc administration in mice, using a modified hot-plate procedure.[20] The erythro racemate **3b** exhibits about fivefold greater potency than methadone (**1**), in contrast to the threo diastereomer **3a**, which is inactive at 50 mg/kg. The activity of **3b** was completely antagonized by prior administration of 0.6 mg/kg of naloxone, supporting the involvement of the same receptor site for both **3b** and **1**. No significant antagonism of **3b** was produced by the prior administration of **3a**, which suggests that **3a** is not competitive with **3b** for the analgetic receptor site and is not acting as a narcotic antagonist.

Stereostructure–Activity Relationship. One plausible explanation for the dramatic potency difference between the erythro (**3b**) and threo (**3a**) racemates may be related to the fact that these diastereomers exhibit profound differences in their conformational behavior as salts rather than as the free bases. There is now good reason to believe[3] that the protonated form is involved in the interaction of analgetic ligands with receptors. Firstly, most if not all strong analgetics exist predominantly in the protonated form at physiological pH. Secondly, evidence has been presented that lipids bearing acidic groups extracted from opiate receptor preparations form salt-like complexes with analgetics and that the stability of the complex parallels the binding of these drugs to analgetic receptors.[21] Thirdly, a very recent study[22] using quaternized analgetics has shown stereoselective binding to opiate receptor preparations. The latter study implicates the charged species in the drug–receptor interaction.

The NMR and pK_a data suggest that the inactive threo racemate **3a**·HCl exists overwhelmingly in a hydrogen-bonded conformation (**20a**). On the other hand, the highly potent erythro racemate **3b**·HCl appears to possess considerable conformational mobility (i.e., comparable mole fractions of **18a–c**) and has less propensity for intramolecular hydrogen bonding.

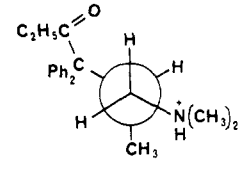
These data are consistent with the idea that **3a**·HCl is inactive because its predominant conformer **20a** does not possess the requisite geometry for efficacious association with analgetic receptors. In contrast, **3b**·HCl offers much greater latitude for effective binding because of its increased conformational flexibility.

When the reported[8] conformational properties of the protonated forms of methadone (**1**·HCl) and isomethadone (**2**·HCl) are analyzed in light of the present study, an intriguing relationship emerges which has an important bearing on the possible identity of the pharmacophoric conformation(s) of diphenylpropylamine analgetics. It had been determined[8] that **1**·HCl exists as a mixture of conformers (**21a–c**) whose composition can be altered with



21a **21b** **21c**

a change of solvent polarity. Two possible internally hydrogen-bonded gauche conformers (**21a,b**) were suggested for **1**·HCl, but the extent of their contribution to the total conformational population could not be determined. Since an x-ray study[23] of (+)-**1**·HBr shows that its geometry approximates an antiperiplanar conformation (**21c**), it seems likely that the difference in $\Delta G°$ between hydrogen-bonded conformations (**21a** and/or **21b**) and **21c** is not substantial. With regard to **2**·HCl, the antiperiplanar-like rotamer **22** has been reported[8] to be highly favored with little, if any, contribution of gauche forms to the population. These results and those of the present



22

study tend to implicate an antiperiplanar arrangement of $^+NHMe_2$ and Ph_2C–COEt for one of the pharmacophoric conformations. Thus, conformationally mobile compounds such as **1**·HCl and **3b**·HCl can readily dispose these groups in such an orientation **22** (favored by isomethadone) because their conformational energy differences apparently are not large. By analogy with **3a**·HCl which resides overwhelmingly in an off-staggered gauche conformation **20a**, it is possible that the gauche rotamers for **3b**·HCl and for **1**·HCl similarly do not possess the proper geometry for effective drug–receptor association.

One additional factor which should be considered is the orientation of the carbonyl group during the drug–receptor interaction. As it is known that an oxygen function at C-3 is required for analgetic activity in the diphenylpropylamine series,[2] it is conceivable that it might be involved in receptor binding, possibly through the

formation of a hydrogen bond. If the carbonyl group in **3a**·HCl were unavailable for binding as a consequence of strong intramolecular hydrogen bonding (**20a**), this also could contribute to its lack of affinity.

If one were to ignore conformational factors and consider the chiral centers in **3a** and **3b** as independent units, it might have been predicted that the more potent optical isomer (5*S*,6*R*) would be found in the threo racemate. This conclusion would have been based on the fact that the more potent enantiomers of methadone (**1**) and isomethadone (**2**) possess the 6*R* and 5*S* configuration, respectively.[24,25] Such a prediction, of course, is not correct because only the erythro racemate (containing the 5*R*,6*R* and 5*S*,6*S* enantiomers) is active. This emphasizes that each chiral center does not behave independently but interacts with other groups to afford a conformational population which strongly influences the potency of the diastereomers.

Finally, since conformational effects are but one facet of the stereostructure–activity relationship, other factors must also be considered in any attempt to fully explain the activity of these compounds. Further studies are currently in progress.

Experimental Section

All melting points are uncorrected. The ir spectra were obtained on either a Perkin-Elmer Model 237B or a Beckmann IR-9 spectrometer and the NMR spectra on a Varian A-60D or XL-100 spectrometer using Me_4Si or DSS as an internal standard. The NMR spectra of **3a**·HCl were run on a Bruker 270-MHz spectrometer at the Southern New England Hi-Field NMR Facility at Yale University. The NMR studies of **3b** were performed on the Varian XL-100. Mass spectra were obtained on either a Perkin-Elmer RMU-6D or AEI MS-30 high-resolution mass spectrometer. GC analyses were carried out on a Perkin-Elmer 900 gas chromatograph. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., and are within ±0.4%.

threo- **and** *erythro*-**3-bromo-2-butanol** were prepared by the method of Winstein and Lucas[26] from pure *cis*- and *trans*-2-butene, respectively.

cis- **and** *trans*-**2-butene oxides (4a,b)** were prepared from the corresponding *threo*- and *erythro*-bromohydrins by the method of Wilson and Lucas[27] and purified to literature values.

trans-**4,5-Dimethyl-3,3-diphenyl-2-iminotetrahydrofuran (5a).** A solution of 109.0 g (0.563 mol) of Ph_2CHCN in C_6H_6 (200 ml) was added dropwise to a stirred mixture of 16.20 g (0.675 mol) of NaH and 100 ml of C_6H_6 under N_2. The temperature was maintained at 45 °C for 6 h after which 40.49 g (0.563 mol) of **4a** was added dropwise at 20 °C. The mixture was stirred for 4 h and then maintained at 45 °C for 12 h. After heating to reflux for 15 min, the cooled mixture was added to H_2O (200 ml) and extracted with C_6H_6. The extract was dried over $MgSO_4$ and concentrated in vacuo. Dissolution of the residual oil in Et_2O and addition of ethereal HCl gave 147.7 g (87.7%) of **5a**·HCl, mp 240 °C dec. The free base was liberated with NaOH, extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. Addition of hexane to the resulting oil gave a solid which was recrystallized from petroleum ether (bp 60–70 °C) to give **5a**: mp 75–77 °C; ir (KBr) 3315 and 1677 cm^{-1}; NMR (CCl_4) δ 0.81 (d, 3 H, *J* = 7.0 Hz, Ph_2CCHCH_3), 1.35 (d, 3 H, *J* = 6.0 Hz, CH_3CHO), 2.81 (m, 1 H, Ph_2CCH_3CH), 3.83 (m, 1 H, CH_3CHO), 7.2 (m, 10 H, C_6H_5). Anal. ($C_{18}H_{19}NO$) C, H, N.

cis-**4,5-Dimethyl-3,3-diphenyl-2-iminotetrahydrofuran (5b)** was prepared as above from 92.6 g (0.48 mol) of Ph_2CHCN, 13.8 g (0.576 mol) of NaH, and 34.52 g (0.48 mol) of **4b**: yield 69.78 g (55%); mp 130–131 °C, after recrystallization from cyclohexane; ir (KBr) 3265 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (d, 3 H, *J* = 7.4 Hz, Ph_2CHCH_3), 1.22 (d, 3 H, *J* = 6.8 Hz, CH_3CHO), 3.24 (m, 1 H, Ph_2CHCH_3), 4.62 (m, 1 H, CH_3CHO), 7.30 (m, 10 H, C_6H_5). Anal. ($C_{18}H_{19}NO$) C, H, N.

threo-2,2-**Diphenyl**-3-**methyl**-4-**hydroxypentanenitrile (6a).** An ethereal solution of 133.42 g (0.503 mol) of **5a** was added to 400 ml of an ethereal solution of CH_3MgI made from 85.6 g (0.603 mol) of CH_3I and 14.7 g (0.603 mol) of Mg turnings. The mixture was heated at reflux for 2 h, cooled, and shaken with 130 ml of saturated aqueous NH_4Cl. The Et_2O layer was separated, extracted with dilute HCl, neutralized with $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed in vacuo to afford 115.90 g (86.8%) of **6a** as a viscous oil which resisted crystallization from a variety of solvents: ir (neat) 3450 and 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (d, 3 H, *J* = 7.0 Hz, Ph_2CCHCH_3), 1.26 (d, 3 H, *J* = 6.3 Hz, CH_3CHO), 1.67 (s, 1 H, OH), 3.04 (m, 1 H, Ph_2CCHCH_3), 3.85 (m, 1 H, CH_3CHO), 7.38 (m, 10 H, C_6H_5). Anal. ($C_{18}H_{19}NO$) C, H, N.

erythro-**2,2-Diphenyl-3-methyl-4-hydroxypentanenitrile (6b).** To 300 ml of an ethereal solution of CH_3MgI, prepared from 58.1 g (0.41 mol) of CH_3I and 9.95 g (0.41 mol) of Mg turnings, was added 90.5 g (0.342 mol) of **5b** in 750 ml of a 2:1 C_6H_6–Et_2O solution. The procedure employed for **6a** was then followed to give 88.75 g (98.2%) of solid **6b**, mp 98–100 °C, which was recrystallized from cyclohexane: ir (KBr) 3500 and 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (d, 3 H, *J* = 7.0 Hz, Ph_2CCHCH_3), 1.19 (d, 3 H, *J* = 6.5 Hz, CH_3CHO), 1.77 (s, 1 H, OH), 2.70 (m, 1 H, Ph_2CCHCH_3), 3.88 (m, 1 H, CH_3CHO), 7.35 (m, 10 H, C_6H_5). Anal. ($C_{18}H_{19}NO$) C, H, N.

threo-**2,2-Diphenyl-3-methyl-4-tosyloxypentanenitrile (7a).** A solution of 9.0 g (0.034 mol) of **6a** and 12.94 g (0.068 mol) of *p*-TsCl in 50 ml of pyridine was allowed to stand for 84 h at 25 °C. The solution was poured into ice water with stirring and the resulting solid filtered, washed with H_2O, and dried. Recrystallization from EtOH gave 11.22 g (80%) of **7a**: mp 149–150 °C; ir (KBr) 2240, 1195, 1180, and 1350 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (d, 3 H, *J* = 6.5 Hz, Ph_2CCHCH_3), ~1.21 (d, 3 H, *J* = 6.5 Hz, CH_3CHO), 2.41 (s, 3 H, $PhCH_3$), 3.39 (m, 1 H, Ph_2CCHCH_3), 4.42 (m, 1 H, CH_3CHO), 7.32 (m, 14 H, C_6H_5 and C_6H_4). Anal. ($C_{25}H_{25}NO_3S$) C, H, N.

Reaction of 7a with Me_2NH. A solution of 7 ml of liquid Me_2NH, 25 mg of $CuSO_4$, and 2.0 g (4.7 mmol) of **7a** was heated in a steel reaction vessel for 48 h at 145 °C. The solution was cooled in dry ice, poured into C_6H_6, washed with H_2O, and extracted wth 2.5 N HCl. The acidic extract was basified with 7 N NaOH, extracted with C_6H_6, and dried over Na_2SO_4. The solvent was removed in vacuo to give a small amount of oil which after crystallization (EtOH–H_2O) gave 0.027 g (1.9%) of solid product, mp 101–102.5 °C, whose ir spectrum was identical with that of **9b**.

Evaporation of the original C_6H_6 layer which remained after extraction with dilute HCl gave 0.81 g of an oil having spectral characteristics consistent with olefin **10**: ir (neat) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (d, 3 H, *J* = 6.8 Hz, CH_3CH), 3.49 (m, 1 H, *J* = 6.8 Hz, CH_3CHCH), ~5.08 (m, 2 H, $C{=}CH_2$), ~5.80 (m, 1 H, $HC{=}CH_2$), 7.20, 7.50 (m, 10 H, C_6H_5). Anal. ($C_{18}H_{17}N$) C, H, N.

erythro-**2,2-Diphenyl-3-methyl-4-tosyloxypentanenitrile (7b)** was prepared by a method identical with that of **7a**. Thus, 20.0 g (0.075 mol) of **6b** and 28.76 g (0.151 mol) of *p*-TsCl in 133 ml of pyridine afforded 26.88 g (85%) of **7b**, mp 166–167.5 °C, after recrystallization ($CHCl_3$–Et_2O): ir (KBr) 2240, 1180, 1174, and 1350 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (d, 3 H, *J* = 6.5 Hz, Ph_2CCHCH_3), 1.40 (d, 3 H, *J* = 6.5 Hz, CH_3CHO), 2.43 (s, 3 H, $PhCH_3$), 2.79 (m, 1 H, Ph_2CCHCH_3), 4.78 (m, 1 H, CH_3CHO), 7.3 (m, 14 H, C_6H_5, C_6H_4). Anal. ($C_{25}H_{25}NO_3S$) C, H, N.

2,2-Diphenyl-3-methyl-4-oxopentanenitrile (8). A total of 28.20 g (0.284 mol) of CrO_3 was added in small portions to 282 ml of pyridine and the mixture stirred at 0 °C until a yellow precipitate formed. A pyridine solution of 30.32 g (0.142 mol) of **6a** was added to the mixture and stirred at 25 °C for 48 h. After addition of 1 l. of Et_2O, the inorganic salts were filtered and the pyridine was removed in vacuo. The residual oil was dissolved in $CHCl_3$, filtered, washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The oil was crystallized from $CHCl_3$–petroleum ether (bp 60–70 °C) to afford 23.38 g (62.5%) of **8**: mp 117–118 °C; ir (KBr) 2240 and 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (d, 3 H, *J* = 7.0 Hz, Ph_2CCHCH_3), 2.10 (s, 3 H, $COCH_3$), 3.79 (q, 1 H, *J* = 7.0 Hz, Ph_2CCHCH_3), 7.40 (m, 10 H, C_6H_5). Anal. ($C_{18}H_{17}NO$) C, H, N.

erythro-**4-Dimethylamino-3-methyl-2,2-diphenylpentanenitrile (9b). Part A.** A solution of 3.6 g (0.019 mol) of $TiCl_4$ in 15 ml of C_6H_6 was added dropwise to a stirred, cooled solution

of 5.14 g (0.114 mol) of Me_2NH and 5.0 g (0.019 mol) of **8** in 75 ml of C_6H_6. After 3 days at 25 °C the solvent was removed in vacuo and 75 ml of THF was added to the residual oil. Sodium borohydride, 3.59 g (0.095 mol), was added followed by dropwise addition of 11.4 ml (0.19 mol) of glacial HOAc. After 2 h the mixture was heated to reflux for 1 h, cooled, and basified with 15% NaOH. Following the addition of 150 ml of H_2O, the mixture was filtered and the filtrate extracted with Et_2O. The extract was dried over Na_2SO_4 and concentrated in vacuo. The resulting oil was crystallized from petroleum ether (bp 60–70 °C) to give 1.72 g (26.4%) of **9b**: mp 101–101.5 °C; GC (1% OV-17 on Chromosorb W, 210 °C) 3.68 min; ir (KBr) 2830, 2735, and 2240 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (d, 3 H, J = 6.8 Hz, Ph_2CCHCH_3), 1.20 (d, 3 H, J = 6.9 Hz, CH_3CHN), 2.08 [s, 6 H, $N(CH_3)_2$], ~2.7 (m, 1 H, Ph_2CCHCH_3), ~2.7 (m, 1 H, CH_3CHN), 7.35, 7.60 (m, 10 H, C_6H_5). Anal. ($C_{20}H_{24}N_2$·HCl) C, H, N.

Part B. Into the upper flask of an apparatus identical with that used for the preparation of **14a** was placed 5.692 g of a 50.6% suspension of NaH (0.12 mol) and 125 ml of dry THF. Recrystallized Ph_2CHCN (23.19 g, 0.12 mol) was dissolved in 40 ml of dry THF and added dropwise to the suspension with stirring. The mixture was heated gently and stirred for 2 h, after which time a deep red color had formed. Into the lower flask was placed 11.70 g (0.10 mol) of **15b** and 75 ml of dry THF. The stirred solution was cooled to 0 °C and 45.5 ml of 2.2 M *n*-BuLi in hexane was slowly injected under N_2. After 15 min, 19.065 g (0.10 mol) of *p*-TsCl in 50 ml of dry THF was added dropwise. The mixture was stirred at 0 °C for 45 min to allow ester formation, after which time the contents of the upper flask were added in one portion. The mixture was brought to 25 °C and allowed to stir for 72 h. The suspension was poured into 1 l. of ice water and extracted three times with Et_2O. The extracts were evaporated under reduced pressure to remove most of the THF and then taken up in Et_2O. The product was extracted into cold 10% HCl; the aqueous extract was back-washed with Et_2O, cooled with ice, and made basic with 15% KOH. The resulting precipitate was taken up in Et_2O and dried ($MgSO_4$) and the solvent removed to afford 23.0 g (79%) of solid which was recrystallized from Et_2O–petroleum ether (bp 60–70 °C) to afford 15.0 g of pure **9b**, mp 101–101.5 °C. Spectra were identical with that prepared above.

Reaction of 9b with EtMgBr. A solution of EtMgBr in 10 ml of Et_2O was prepared from 0.93 g (0.0085 mol) of EtBr and 0.208 g (0.0085 g-atom) of Mg. The volume was reduced to 5 ml by gentle heating. Xylene (10 ml) was then added and the temperature was raised to 110 °C. This was followed by dropwise addition of a solution of 0.250 g (0.85 mmol) of **9b** in xylene (5 ml) and the temperature was maintained at 120 °C for 7.5 h. The reaction mixture was cooled, H_2O added and then Et_2O, and the mixture extracted. The Et_2O extract was washed with H_2O, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The resultant oil (0.249 g) was determined by TLC (alumina; C_6H_6–petroleum ether) to be a mixture of two compounds (R_f 0.5 and 0.9) and its ir spectrum showed no CN or CO absorptions. The higher R_f product was shown by NMR to be olefinic and was not investigated further. The lower R_f product was isolated by acid extraction of an Et_2O solution of the crude reaction product, followed by basification, Et_2O extraction, drying over Na_2SO_4, and evaporation of solvent. A homogeneous oil (0.134 g) was obtained, the spectrum of which was consistent with the decyanated product **12**: NMR δ 0.87 (d, 3 H, J = 7.0 Hz, Ph_2CCHCH_3), 0.92 (d, 3 H, J = 6.8 Hz, CH_3CHN), 2.17 (s, 6 H, NMe_2), ~2.48 [m, 2 H, $CH(CH_3)CH(CH_3)$], 4.14 (d, 1 H, J = 9.5 Hz, Ph_2CH), 7.30 (m, 10 H, C_6H_5). Repeated attempts to obtain an analytically pure HCl salt were unsuccessful. The same product was obtained when **9b** was treated with EtLi at 25 °C or above.

***erythro*-2,2-Diphenyl-3-methyl-4-dimethylaminopentanamide (13b).** A solution of 10.0 g (0.034 mol) of **9b** and 66% H_2SO_4 (200 ml) was heated at 115 °C under N_2 for 88 h, after which time no nitrile absorption was visible in the ir. The solution was cooled with ice and carefully neutralized with 40% KOH. The precipitate was extracted with four portions of CH_2Cl_2 which was dried over Na_2SO_4 and evaporated to afford 10.38 g (98%) of impure solid. The crude product was triturated with hot Et_2O several times, which left 1.5 g of residual side product. Concentration of the solution afforded 7.55 g (71%) of **13b** as colorless needles: mp 143.5–144 °C; ir (KBr) 3280, 2850, 2790, and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (d, 3 H, J = 7.2 Hz, Ph_2CCHCH_3), 1.41 (d, 3 H, J = 7.2 Hz, CH_3CHN), 1.97 (s, 6 H, NMe_2), ~2.74 (m, 2 H, Ph_2CCHCH_3 and CH_3CHN), 6.0 (br s, 2 H, NH_2), 7.20 (m, 10 H, C_6H_5). Anal. ($C_{20}H_{26}N_2O$) C, H, N.

Methyl *erythro*-2,2-Diphenyl-3-methyl-4-dimethylaminovalerate (14b). A stirred solution of 3.824 g (12.3 mmol) of **13b** in glacial HOAc (75 ml) was saturated with gaseous HCl. The solution temperature was maintained at 45 °C throughout the reaction. With the aid of an infusion pump, 25 ml of freshly distilled *n*-BuONO was added over 6 h and the red solution was allowed to stir overnight. *n*-BuONO (25 ml) was again infused over 12 h and again the reaction was stirred overnight. The process was repeated a third time, at which point only a trace of **13b** remained by ir.

The pale yellow solution was evaporated under reduced pressure to afford a yellow oil. The oil was taken up in dry MeOH, to which was added ethereal CH_2N_2 to excess. After standing 4 h, the solution was extracted with 10% HCl. The aqueous solution was back-extracted with Et_2O, maintained at 5 °C, and neutralized with 40% KOH. The resulting precipitate was extracted into Et_2O, dried over $MgSO_4$, and evaporated to afford 2.96 g of crude **14b**. The oil was purified by column chromatography on basic Al_2O_3 (activity I), eluting with 30% $CHCl_3$–hexane to afford 2.465 g (61.5%) of pure **14b** which solidified upon standing. The product was recrystallized from Et_2O–hexane: mp 111–112 °C; ir (neat) 2830, 2775, and 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 7.0 Hz, Ph_2CCHCH_3), 1.02 (d, 3 H, J = 7.0 Hz, CH_3CH_2N), 2.15 (s, 6 H, NMe_2), 2.18 (m, 1 H, Ph_2CCHCH_3), 3.27 (m, 1 H, CH_3CHN), 3.67 (s, 3 H, OCH_3), 7.35 (m, 10 H, C_6H_5). **18b**·HCl had mp 183.5–184 °C. Anal. ($C_{21}H_{27}NO_2$·HCl) C, H, N.

***erythro*-4,4-Diphenyl-5-methyl-6-dimethylamino-3-heptanone (*erythro*-5-Methylmethadone) (3b).** Into 40 ml of anhydrous Et_2O (dried over Na) was shaved 0.268 g (0.0386 g-atom) of Li wire under N_2. The stirred mixture was cooled to −40 °C and 2.108 g (19.4 mmol) of purified EtBr added dropwise. More Et_2O and EtBr were added periodically to ensure complete reaction of the Li. After 3 h, no Li remained. Ester **14b** (0.817 g, 2.5 mmol) in anhydrous Et_2O was slowly added to the EtLi solution. After addition was complete, the solution was allowed to warm to 0 °C where it was held for 6 h and then stored at 5 °C for 24 h. The solution was poured into vigorously stirred ice water (700 ml) and extracted with Et_2O. The product was taken up in 10% HCl which was then cooled and neutralized with 15% KOH. The resulting precipitate again was extracted with Et_2O, which was dried over $MgSO_4$ and evaporated to afford 0.784 g (94%) of an oil. The product was purified by column chromatography on Al_2O_3 (activity I), eluting with 50% $CHCl_3$–hexane to afford 0.557 g of **3b** as a viscous oil: ir (neat) 2830, 2775, and 1705 cm^{-1}; NMR ($CDCl_3$) 0.70 (t, 3 H, J = 7.0 Hz, CH_3CH_2), 0.85 (d, 3 H, J = 6.8 Hz, Ph_2CCHCH_3), 0.92 (d, 3 H, J = 6.8 Hz, CH_3CHN), 2.02 [s, 6 H, $N(CH_3)_2$], 2.28 (q, 2 H, J = 7.0 Hz, CH_3CH_2), ~2.20 (m, 1 H, J = 7.2 Hz, Ph_2CCHCH_3), 3.26 (m, 1 H, J = 7.2 Hz, CH_3CHN), 7.45 (s, 10 H, C_6H_5). **3b**·HCl had mp 223–224 °C dec. Anal. ($C_{22}H_{29}NO$·HCl) C, H, N.

***erythro*-3-Dimethylamino-2-butanol (15b).** A solution of 10.0 g of **4b**, 13 ml of liquified Me_2NH, and 2 drops of 12 N HCl was placed in a Parr pressure bomb and heated in a steam bath for 7 h. The contents were cooled, diluted with Et_2O (50 ml), washed with saturated $NaHCO_3$, and dried over Na_2SO_4. Evaporation of solvent and distillation afforded 8.39 g (52%) of **15b**, bp 154–156 °C (lit.[17] 152.5–153.5 °C).

***threo*-3-Dimethylamino-2-butanol (15a)** was prepared from 10 g of **4a** in an analogous manner to afford 11.6 g (71%) of **15a**: bp 138–140 °C (lit.[17] 141–142 °C).

Methyl *threo*-2,2-Diphenyl-3-methyl-4-dimethylaminovalerate (14a). Into a dry, three-neck flask modified for downward addition and fitted with a mechanical stirrer, N_2 inlet, septum, and drying tube was placed 11.0 ml of 5.07% CH_3Li in Et_2O. The Et_2O was evaporated under a stream of dry N_2 and the resulting solid was redissolved in 10 ml of dry THF. To this solution was added 4.40 g (0.0188 mol) of Ph_3CH in 10 ml of dry THF. The solution was stirred for 2 h, forming a deep red color. Enough $Ph_2CHCOOMe$ in THF was added to just discharge the red color (1.858 g, 8.2 mmol) and form an orange solution. Into a second dry, three-neck flask fitted to the bottom of the above apparatus, to which was attached an additional funnel with N_2

inlet, injection septum, and drying tube, was placed 0.958 g (8.2 mmol) of **15a** in 10 ml of dry THF. To the cooled solution (0 °C) was injected dropwise 4.32 ml (8.2 mmol) of *n*-BuLi (1.9 M in hexane). After stirring for 10 min, 1.568 g (8.2 mmol) of *p*-TsCl in 10 ml of dry THF was added dropwise. The solution was stirred for 45 min.

The contents of the upper flask were added to the lower flask, after which the yellow mixture was brought to 25 °C and allowed to stir for 18 h. The pale yellow suspension was poured into 100 ml of ice-water and extracted with four portions of Et_2O. The extracts were combined and dried over $MgSO_4$, and the solvent was removed. The residual oil was taken up in 100 ml of Et_2O and extracted three times with cold 10% HCl. This aqueous acidic solution was washed twice with Et_2O, cooled, and made basic with 15% KOH. The resulting precipitate was extracted with four portions of Et_2O, which were combined, dried over $MgSO_4$, and evaporated to afford 1.216 g (46%) of product as a yellow oil. The product was distilled, bp 155–158 °C (0.15 mm), to afford a yellow glass: ir (CCl_4) 2820, 2780, and 1730 cm^{-1}; NMR (CCl_4) δ 0.56 (d, 3 H, J = 6.8 Hz, Ph_2CCHCH_3), 0.77 (d, 3 H, J = 6.5, CH_3CHN), 2.12 (s, 6 H, NMe_2), ~2.2 (m, 1 H, Ph_2CCHCH_3), ~3.2 (m, 1 H, CH_3CHN), 3.40 (s, 3 H, OCH_3), 7.3 (m, 10 H, C_6H_5). **14a**·HCl had mp 184–185 °C. Anal. ($C_{21}H_{27}NO_2$·HCl) C, H, N.

threo-**4,4-Diphenyl-5-methyl-6-dimethylamino-3-heptanone (*threo*-5-methylmethadone, 3a)** was prepared in a manner analogous to **3b** from 1.272 g (0.392 mmol) of **14a**, 0.284 g (0.0041 g-atom) of Li wire, and 2.240 g (2.10 mmol) of purified EtBr to afford 1.211 g (96%) of **3a** as a pale yellow solid. Recrystallization from Et_2O–petroleum ether (bp 60–70 °C) afforded **3a**: mp 109.5–111.0 °C; ir (KBr) 2825, 2780, and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.38 (d, 3 H, J = 6.6 Hz, Ph_2CCHCH_3), 0.71 (t, 3 H, J = 7.5 Hz, CH_3CH_2–), 0.78 (d, 3 H, J = 7.0 Hz, CH_3CHN), 2.20 (s, 6 H, NMe_2), ~2.4 [m, 3 H, CH_3CH_2 (J = 7.5 Hz) and Ph_2CCHCH_3 ($J \leq 1$ Hz)], ~3.3 (m, 1 H, $J \leq 1$ Hz, CH_3CHN), 7.3 (m, 10 H, C_6H_5). Anal. ($C_{22}H_{29}NO$) C, H, N. **3a**·HCl had mp 214–215 °C.

Apparent dissociation constants were determined on the HCl salts in aqueous MeOH as described previously.[6]

Biological testing was performed using a modified hot-plate test of Eddy,[28] as described previously,[20] using a group of ten male Swiss–Webster mice for each dose level examined. The drugs were administered subcutaneously in normal saline solution and the reaction times determined after 15 min. ED_{50} values were determined by probit analysis, according to the method of Stanley.[29]

Acknowledgment. The authors wish to acknowledge support of this work in the form of NIH Research Grant NS05192, an NIH postdoctoral fellowship (to J.G.H), and an NIH predoctoral fellowship (to E.P.B.). We also express our thanks to Professor R. G. Lawler for helpful discussions and to the Southern New England High Field NMR Facility for the 270-MHz spectra. We are also grateful to Dr. Richard Newmark for some of the 100-MHz decoupling experiments and to Professor A. E. Takemori for the naloxone used for competitive antagonism studies.

References and Notes

(1) For paper 20, see D. F. Fries and P. S. Portoghese, *J. Med. Chem.*, **19**, 1155 (1976).
(2) P. A. J. Janssen, "Synthetic Analgesics, Part I", Pergamon Press, New York, N.Y., 1960.
(3) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
(4) P. S. Portoghese, *Annu. Rev. Pharmacol.*, **10**, 51 (1970).
(5) N. B. Eddy and E. L. May, *Science*, **181**, 407 (1973).
(6) P. S. Portoghese and D. A. Williams, *J. Med. Chem.*, **12**, 839 (1969).
(7) P. S. Portoghese and D. A. Williams, *J. Med. Chem.*, **13**, 626 (1970).
(8) J. G. Henkel, K. H. Bell, and P. S. Portoghese, *J. Med. Chem.*, **17**, 124 (1974).
(9) N. R. Easton, J. H. Gardner, and J. R. Stevens, *J. Am. Chem. Soc.*, **69**, 2941 (1947).
(10) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).
(11) R. F. Borch and H. D. Durst, *J. Am. Chem. Soc.*, **91**, 3996 (1969); R. F. Borch, M. D. Bernstein, and H. D. Durst, *ibid.*, **93**, 2897 (1971).
(12) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).
(13) A. A. Larson, B. F. Fuller, B. Elpern, and J. S. Buck, *J. Am. Chem. Soc.*, **70**, 4194 (1948).
(14) M. E. Specter, L. C. Cheney, and S. B. Binkley, *J. Am. Chem. Soc.*, **72**, 1659 (1950).
(15) A. W. Ruddy, *J. Am. Chem. Soc.*, **73**, 4096 (1951), and references cited therein.
(16) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **9**, 603 (1966).
(17) E. E. Smissman, W. L. Nelson, J. B. LaPidus, and J. L. Day, *J. Med. Chem.*, **9**, 458 (1966).
(18) L. M. Jackman and S. Sternhall, "Applications of Nuclear Magnetic Resonance Spectroscopy in Orgranic Chemistry", 2d ed, Pergamon Press, New York, N.Y., 1969, Chapter 4-2.
(19) J. F. King in "Techniques of Organic Chemistry", Part I, Vol. XI, Interscience, New York, N.Y., 1963, Chapter VI, p 318.
(20) P. S. Portoghese, Z. S. Gomaa, D. L. Larson, and E. Shefter, *J. Med. Chem.*, **16**, 199 (1973).
(21) H. H. Loh, T. M. Cho, Y. C. Wu, R. A. Harris, and E. L. Way, *Life Sci.*, **16**, 1811 (1975).
(22) K. E. Opheim and B. M. Cox, *J. Med. Chem.*, **19**, 857 (1976).
(23) A. W. Hanson and F. R. Ahmed, *Acta Crystallogr.*, **11**, 724 (1958).
(24) A. H. Beckett and A. F. Casy, *J. Chem. Soc.*, 900 (1955).
(25) A. H. Beckett, G. Kirk, and R. Thomas, *J. Chem. Soc.*, 1386 (1962).
(26) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939).
(27) C. Wilson and H. Lucas, *J. Am. Chem. Soc.*, **58**, 2397 (1936).
(28) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953).
(29) J. Stanley, "The Essence of Biometry", McGill University Press, Montreal, 1963, p 127.