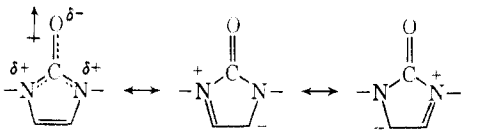
present data indicate a similarity between chlorpromazine and the imidazolidinones (cyclic ureas), a similar effect on membrane permeability is possible. To account for the lower than expected activities for a number of compounds examined (see Figure 1) one may apply the classical lock and key theory. If a molecule must fit into a depression in the membrane in order for effective binding to occur, then excess lengthening of the molecule could prevent it from fitting into the receptor site and therefore inactivate it. This agrees with the finding that increasing the alkyl length from 2 to 3 C decreases activity less than changing from *meta* to *para* substitution,[3] since the three-dimensional tetrahedral bond of the $CH_2$ group adds less horizontal length to the molecule than the linear bond of the *p*-X-Ar substituent. Similarly, the fact that changing $Me_2N$ to $Et_2N$ does not lengthen the molecule too much, as shown by the activities, is also in accordance with this explanation. A conformation with a six-membered cyclic ion–dipole interaction or a seven-membered ring through the $\geqslant NH^+ \cdots {}^-O-$ bridge may be fairly stable; however, this conformation may retard the dipole–dipole interaction with the receptor. Another more probable conformation may have the protonated N and the partially positive urea N extended as far apart as possible. It is conceivable from the second conformation that by extending the alkylene side chain from 2 to 3 carbons or by putting a substituent at the *para* position of the benzene ring this molecule might be rendered too long to fit into the receptor.

The inactivity of the unsaturated imidazolin-2-ones[6] could be due either to the faster biotransformation of the double bond or to the introduction of resonance into the ring, thus altering the dipole moment of the urea grouping:[7b]



While the preceding discussion is highly speculative, it offers a seemingly viable explanation for the anomalies observed. Outside of these the lipohydrophilic character is the predominant factor controlling the relative potency for this group of CNS depressants. In the future it will be interesting to increase the partition coefficient to log $P_0$ and beyond to see if more potent depressants can be obtained. This might be done by adding a larger alkyl group to the 4 or 5 position of the imidazolidinone, by adding larger alkyl group to the meta position of the benzene ring, or by making α-naphthyl derivatives instead of the benzene derivatives.

**Acknowledgment.** The authors express their thanks to W. B. Wright, Jr., Lederle Laboratories, Pearl River, N. Y., for a sample of 1-(2-dimethylaminoethyl)-3-(*m*-methoxyphenyl)-2-imidazolidinone hydrochloride used in the measurement of the partition coefficient, and to the Computer Science Laboratories of this university for data processing.

# Stereochemical Studies on Medicinal Agents. VIII.[1] Absolute Stereochemistries of Isomethadol Isomers[2,3]

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*Received March 2, 1970*

The absolute stereochemistries of optically active α- and β-isomethadol diastereomers have been deduced by the asymmetric induction procedure of Prelog. The dissociation constants of the title compounds and isomethadone suggest the absence of intramolecular $+N-H\cdots O$ in aq medium. Ir data indicate that both diastereomers are internally bonded in $CCl_4$ and that the α isomer is more strongly H bonded. Results from nmr studies support the ir data and are consistent with conformations **11a** and **12a** in $CDCl_3$. The fact that only one isomer (3*S*,5*S*) possesses high potency suggests that the proper combination of configurations is necessary. The possible influences of conformational isomerism on analgetic activities are discussed. It is proposed that the potency differences between enantiomers are due primarily to the obstructive role of the 5- or 6-Me groups of (+)-isomethadone and (+)-methadone.

We have reported[1] previously on the absolute stereochemistries of α- and β-methadol enantiomers and have offered an explanation for the inversion of receptor stereoselectivity at the C-6 asymmetric center of these diastereomeric analgetics. As a continuation of our interest in this area, we have investigated[3] a group of closely related compounds derived from reduction of isomethadone (**1**).[5-7]

These diastereomers, commonly known as α- and β-isomethadol (**2**), have been prepared in their optically active forms by May and Eddy.[7] It is noteworthy that the analgetically active alcohol (+)-β-**2** and the more potent acetate esters [(−)-β-**3**, (+)-α-**3**] all are configurationally related at C-5 since they were derived from (−)-isomethadone (Table I).

(1) Part VII of this series: P. S. Portoghese and D. A. Williams, *J. Med. Chem.*, **12**, 839 (1969).

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

(3) For a preliminary report on this work, see P. S. Portoghese and D. A. Williams, *Tetrahedron Lett.*, 6299 (1966).

(4) Predoctoral Fellow 5-FI-GM 20515, 1963-1966.

(5) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 663 (1948).

(6) M. Speeter, W. Byrd, L. Cheney, and S. Brinkley, *J. Amer. Chem. Soc.*, **71**, 57 (1949).

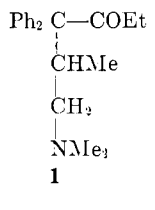
(7) E. L. May and N. B. Eddy, *J. Org. Chem.*, **17**, 1210 (1952).

TABLE I

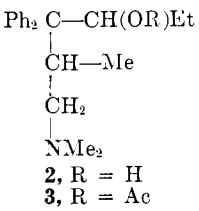
ANALGETIC ACTIVITIES[a] OF ISOMETHADONE, ISOMETHADOLS, AND ACETYLMETHADOLS

| 1 | $ED_{50}$ (mg/kg) | 2 | $ED_{50}$ (mg/kg) | 3 | $ED_{50}$ (mg/kg) |
|---|---|---|---|---|---|
| 5*R* | 49.8 | (+)-α | 60.7 | (−)-α | 62.7 |
| | | (−)-β | 58.7 | (+(-β | 70.6 |
| 5*S* | 1.2 | (−)-α | 91.7 | (+)-α | 2.7 |
| | | (+)-β | 6.2 | (−)-β | 10.9 |

[a] Analgetic activities were obtained from ref 7.



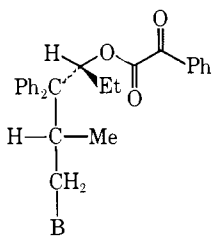
**1**



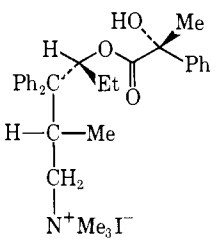
**2**, R = H
**3**, R = Ac

In this report, the complete stereochemical assignment of the isomethadol isomers are presented and the possible roles of groups attached to the C-3 and C-5 asymmetric centers of these compounds in the drug–receptor interaction are discussed.

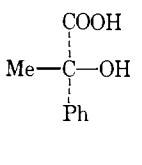
**Chemistry.**—The procedure of Prelog[8] was employed for determination of the absolute configuration at C-3. Treatment of (−)-α-isomethadol with benzoylformyl chloride yielded the corresponding benzoylformate ester (**4**·HCl). Because of our prior experience[1] with esters of this type forming pyrrolidinium salts due to neighboring group participation of the basic nitrogen, we converted **4** into the methiodide **5**. Reaction of **5** with MeMgI, stereoselectively afforded **6** which was saponified without isolation to give (*R*)-(−)-atrolactic acid (**7**) (67% overall yield based on **5**) in 25% optical purity.



**4**, B = $NMe_2$
**5**, B = $N^+Me_3I^-$

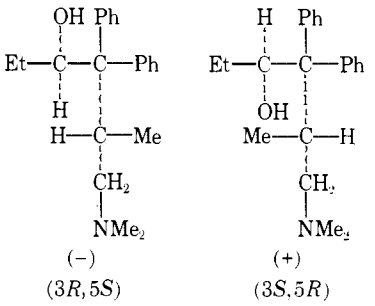


**6**

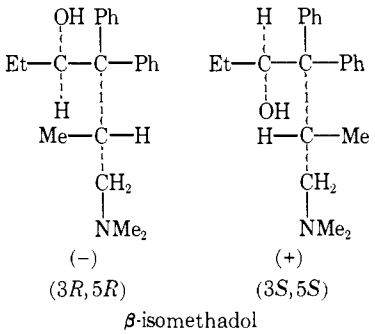


**7**

According to Prelog's rule,[8] the large (diphenylalkyl), medium (ethyl), and small (hydrogen) groups attached to C-3 should be in the sequence depicted by formula **5** in order to give rise to a preponderance of epimeric ester **6**. The configuration at the C-3 center of (−)-α-**2** therefore is assigned to the *R* series. Since (−)-α-isomethadol is derived from (−)-isomethadone, whose configuration[9] is 5*S*, the complete stereochemistry is designated as (3*R*,5*S*) [(−)-**8**]. The epimeric compound, (+)-β-isomethadol [(+)-β-**2**], also is obtained from (−)-isomethadone and hence possesses the (3*S*,5*S*) [(+)-**9**] configuration. By virtue of their enantiomeric relationship to the preceding compounds, (+)-α- and (−)-β-isomethadol are assigned the (3*S*,5*R*) [(+)-**8**] and (3*R*,5*R*) [(−)-**9**] configurations, respectively.



**8**



**9**

**p$K_a$ Studies.**—It might be expected on electronic grounds[10] that the dissociation constants for isomethadone and methadone would be similar. However, our p$K_a$ values (Table II) and those reported by Marshall[11] indicate methadone to be considerably more basic. It can be noted further than the isomethadol diastereomers and 3-deoxymethadone all have p$K_a$ values which are close to that of isomethadone. The enhanced basicity of methadone has been attributed[1] to stabilization of the conjugate acid by internal H bonding of the type, +N—H...O=C. Steric factors are most likely responsible for the lower basicity of isomethadone-type compounds, and projection formulas **10a–c** suggest this is due to a low population of rotamers capable of internal association. The preferred dihedral relationship of the C-4,5 centers should have the C-5 proton staggered between the two phenyl groups, since all other possible staggered arrangements at these centers would be highly unfavorable. In order for intramolecular H bonding to occur, the +$NH(CH_3)_2$ group must be *gauche* to the bulky $Ph_2CO$–Et moiety (**10a,b**). However, these conformations would be destabilized by the *gauche* interaction of the +$NH(CH_3)_2$ group with both the 5-Me and $Ph_2CO$–Et substituents in

TABLE II

APPARENT DISSOCIATION CONSTANTS FOR ISOMETHADONE AND RELATED COMPOUNDS

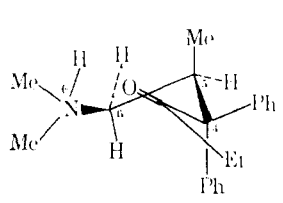
| Compound | p$K_a$ |
|---|---|
| Isomethadone | 7.77 |
| α-Isomethadol | 7.77 |
| β-Isomethadol | 7.76 |
| Methadone | 8.62 |
| 3-Deoxymethadone | 7.93 |

(8) V. Prelog, *Helv. Chem. Acta*, **36**, 308 (1953); V. Prelog and H. Meier, *ibid.*, **36**, 320 (1953); W. G. Dauben, D. F. Dickel, O. Jeger, and V. Prelog, *ibid.*, **36**, 325 (1953); V. Prelog, E. Philbin, E. Watanabe, and M. Wilhelm, *ibid.*, **39**, 1086 (1956).

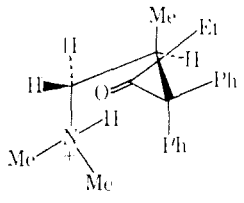
(9) A. H. Beckett, G. Kirk, and R. J. Thomas, *J. Chem. Soc.*, 1386 (1962).

(10) D. Perrin, *Quart. Rev.*, **18**, 295 (1964).

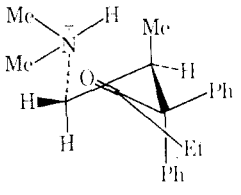
(11) P. B. Marshall, *Brit. J. Pharmacol.*, **10**, 270 (1953).



10a



10b



10c

**10a**, and with $Ph_2CO$–Et in **10b**. Molecular models reveal that the latter conformer, although less hindered than the former, would be incapable of forming a strong intramolecular H bond because of the greater distance and difficulty of achieving colinearity between H—N+ and C=O. The remaining staggered conformer (**10c**), which has the two large groups 180° apart, is least hindered but not capable of internal association. The highly unfavorable steric interactions undoubtedly are great enough so that **10a** and **10b** are not important contributors to the rotameric population. Thus, it would be reasonable to expect a high population of **10c** in aqueous medium and this would be reflected by a lower basicity relative to methadone.

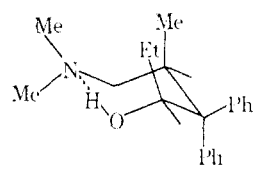
**Ir Studies.**—The high resolution ir spectra of 0.5 *M* solutions ($CCl_4$) of both isomethadol bases revealed a very weak free OH band at 3580 $cm^{-1}$. Absorptions corresponding to bonded OH appeared in the 3000-$cm^{-1}$ region and at 3225 $cm^{-1}$ for the $\alpha$ and $\beta$ isomers, respectively. A more exact frequency assignment for the former could not be made because of interference by CH absorption bands. The 0.005 *M* spectra of the bases showed only a very small increase in the intensity of the free OH band and no significant change in bonded OH absorption. The absence of a significant concentration dependency suggests that both diastereomers are internally H bonded in nonpolar solvent. The strong internal H bonding might be related to the fact that these isomers possess the optimal number of C atoms between OH and amine functions.[12] It appears that the $\beta$ isomer is less strongly associated, since its bonded OH absorbs at higher frequency than that of the $\alpha$ isomer.[13] It is unlikely that significant populations of the internally bonded bases are present in aqueous medium because water would solvate the H bonding moieties. This is suggested by the inability of the conjugate acids to be internally bonded in polar solvent.

**Nmr Studies.**—The OH proton resonances of $\alpha$- and $\beta$-isomethadol bases ($CDCl_3$) were seen as singlets at $\delta$ 4.2 and 5.2, respectively. The fact that these chemical shifts are located at much higher field than those reported ($\delta \sim 8$)[1] for methadol diastereomers is consistent with there being weaker H bonds in the isomethadols. This can be attributed to steric hindrance of the type described for isomethadone (**10**) earlier in this report.

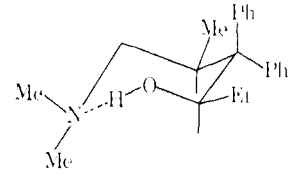
(12) A. B. Foster, A. H. Haines, and M. Stacey, *Tetrahedron*, **16**, 177 (1961).

(13) R. M. Badger and S. H. Bauer, *J. Chem. Physics*, **5**, 839 (1937).

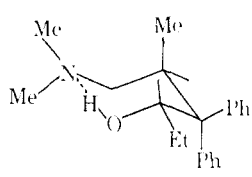
The −40° spectrum ($CDCl_3$) of $\alpha$-isomethadol displayed the OH proton resonance as a doublet ($J$ = 9 cps) at $\delta$ 3.8. Under identical conditions the $\beta$ isomer exhibited this proton resonance as a broadened singlet ($\delta$ 6.3, $W_H$ = 10 cps). If all staggered H bonded conformations (**11**, **12**) for the diastereomers are assumed, the doublet for the $\alpha$ isomer is consistent with there being a preponderance of the conformer **11a** containing a transoid CH–OH[14] arrangement. The preference for **11a** may be due to the highly unfavorable interaction arising from the flanking of the 3-Et and 5-Me groups by the phenyl substituents when in conformation **11b**. Barton has reported[15] similar effects in cyclohexane systems. Moreover, molecular models reveal that "diaxial" type interaction between the C-3 and C-5 substituents in **11a** should be lower in energy when compared to a similarly substituted cyclohexane because the former possesses greater flexibility. The presence of a singlet for the $\beta$ isomer is consistent with a *gauche* CH–OH relationship (**12a**) since such coupling has been reported to be in the vicinity of 2 cps.[14] The absence of an observable doublet suggests that at −40° the proton exchange rate is too rapid for coupling of that magnitude to be detected. Molecular models suggest no obvious explanation as to why **12a** should be favored over **12b**.



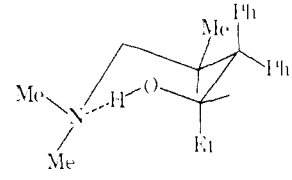
11a



11b



12a



12b

The effect of temperature on the OH chemical shift of $\alpha$- and $\beta$-isomethadol is illustrated in Figure 1. The small but significant difference in the slopes suggests[1,16] that the $\alpha$ isomer is more strongly H bonded. This is also consistent with the ir studies.

The greater propensity of the $\alpha$ isomer to form an intramolecular H bond may be rationalized on the basis of perspective formulas **11a** and **12a**. In **11a** neither the 3-Et nor the 5-Me substituents are flanked by the phenyl groups, whereas this is not the case for **12a**. The severe nonbonded interaction caused by the flanking of the ethyl substituent would mean that the conformation **12a** which is amenable to internal H bonding would be of higher energy than that of **11a** and therefore be more weakly associated.

**Stereostructure–Activity Relationship.**—The fact that only one of the 4 possible isomethadol isomers is a potent analgetic (Table I) suggests that high activity is dependent on the "correct" combination of configura-

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

(15) D. H. R. Barton, *Chem. Ind.*, 661 (1953).

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

tions at two asymmetric centers. This is in contrast with the methadol isomers[17] where the configuration at only one asymmetric center (C-3) is of primary importance.[1,18,19] The stereochemical feature common to all of the more potent isomers of isomethadol, methadol,[1,18] and 6-desmethylmethadol[19] is the 3*S* configuration. The C-5 stereochemistry of β-(+)-**2** [(+)-**9**] is equivalent to that found in the more active isomers of a variety of related analgetics (**13**–**18**).[9,20]

R
|
H—C—Me
|
$CH_2$
|
B

**13**, R = $Ph_2CCOEt$; B = $NMe_2$
**14**, R = $Ph_2CCOEt$; B = $NC_4H_8O$
**15**, R = Ph-NCOEt; B = $NC_5H_{10}$
**16**, R = $PhCH_2(Ph)COCOEt$; B = $NMe_2$
**17**, R = $Ph_2CCONC_4H_8$; B = $NC_4H_8O$
**18**, R = $Ph_2CCONC_4H_8$; B = $NC_5H_{10}$

Acetylation relegates the C-3 center to a relatively minimal stereochemical role in the drug–receptor interaction, whereas the C-5 asymmetric center retains its importance. Hence, the more active esters, α-(+)-**3** and β-(−)-**3** (Table I), are stereochemically identical at C-5 but possess opposite configurations at C-3. This situation, which was also noted among the acetylmethadols,[1] may be explained by assuming that the OH group functions as a proton donor in H bonding to the receptor. In this regard, the acetoxy group would be incapable of functioning in this fashion and therefore might behave as a proton acceptor if H bonding also plays a role in the binding of the esters to the receptor. The fact that high stereoselectivity is associated with the OH but not with the acetate group, suggests that these H bonding functions are associated with proton acceptor or donor dipoles located in dissimilar topographic environments on the same receptor. Alternately, the active isomers of isomethadol and acetylisomethadol may each be binding to different types of analgetic receptors having different stereoselectivities.[21]

It is significant that there are numerous examples[1,21] of inversion of receptor stereoselectivity at C-6 or at an equivalent center among structures related to methadone, while there are no known cases of this occurring in compounds having an asymmetric center at C-5 or its equivalent in analgetics related to isomethadone (**13**–**18**).[20] Could this be due in part to differences in conformational mobility between methadone-type and isomethadone-type compounds? As a general rule it would be expected that the conformational mobility about a critical asymmetric center would determine the likelihood of inversion of receptor stereoselectivity. A comparison of projection formulas of compounds in the isomethadone series (**19**) with those related to methadone (**20**) makes it apparent that the former are more conformationally restricted about the C-4,5 bond than the latter. Thus it is probable that rotamer **20a**, **20b**, or both may be involved in the receptor interaction. In such a situation the constitution of the R group would determine which conformer would be most readily accepted by the receptors. For example, the transition from 6*R* to 6*S* receptor stereoselectivity on conversion of methadone into α-methadol can be attributed to different conformational modes of binding to the receptors.[1] On the other hand, the high conformational homogeneity of **19** might preclude contribution of a significant fraction of an unfavored C-4,5 rotamer (*e.g.*, one which has the 5-Me group flanked by the phenyl rings) in the receptor interaction, and thereby make alternate modes of binding less likely.

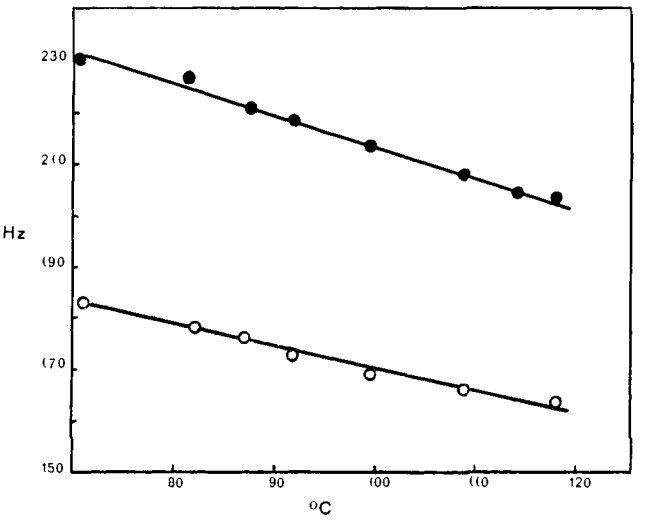
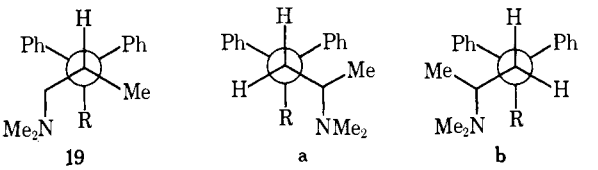



Figure 1.—The temperature dependence of the OH proton resonance for α-isomethadol (○) and β-isomethadol (●) in $C_2Cl_4$.




R = COEt
R = CH(OH)Et
R = CH(OAc)Et

In addition to the aforementioned factors, the absence of inversion of receptor stereoselectivity in isomethadone-type compounds (**13**–**18**) may signify that receptor topography in proximity with the C-5 center is more demanding than the receptor components in the vicinity of C-6. This would imply that there would be a greater possibility for differing modes of interaction in methadone-related compounds.

The potency differences between enantiomers are very likely due primarily to the obstructive role of the 5- or 6-Me groups in the less active (+) isomers inasmuch as desmethylmethadone, (−)-methadone, and (−)-isomethadone all have comparable potencies.[22] Whether this is due to steric hindrance between the Me group and the receptor, to intramolecular steric hindrance (*i.e.*, methyl-induced stabilization of a particular conformation which does not allow facile drug–receptor association), or a combination of these possibilities, is difficult to ascertain at this time.

(17) N. B. Eddy and E. L. May, *J. Org. Chem.*, **17**, 321 (1952).
(18) P. S. Portoghese and D. A. Williams, *J. Pharm. Sci.*, **55**, 990 (1966).
(19) A. F. Casy and M. M. A. Hassan, *J. Med. Chem.*, **11**, 601 (1968).
(20) H. R. Sullivan, J. R. Beck, and A. Pohland, *J. Org. Chem.*, **28**, 2381 (1963); P. S. Portoghese, *J. Med. Chem.*, **8**, 147 (1965); P. Crabbe, P. Demoen, and P. Janssen, *Bull. Soc. Chim. Fr.*, 2855 (1965); A. F. Casy and M. M. A. Hassan, *J. Chem. Soc.*, 683 (1966).
(21) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966), and ref cited therein.
(22) D. G. Leimbach and N. B. Eddy, *J. Pharmacol. Exp. Ther.*, **110**, 135 (1954).

## Experimental Section[23]

**(+)-α-Isomethadol Benzoylformate Methiodide (5).**—A mixture of (−)-α-isomethadol[7] (0.79 g, 0.0016 mol) and 0.7 g of benzoylformyl chloride in 20 ml of EtOAc was refluxed for 10 hr. The solvent was removed *in vacuo* to afford an oily residue which resisted attempts at crystallization. A cooled EtOAc solution (10 ml) containing 0.2 g of this oil was shaken with 0.2 g of $Ag_2O$ for 15 min. Excess MeI was added to the filtrate and cooled overnight to yield 0.3 g (82%) of **5**, mp 198–200° dec, $[\alpha]D$ +22.5° (*c* 0.4, MeOH), after recrystallization (MeOH). *Anal.* ($C_{30}H_{36}INO_3$) C,H,N.

**(+)-α-Isomethadol Benzoylformate Methiodide and Methylmagnesium Iodide.**—A fivefold excess of MeMgI and 0.28 g (0.00048 mol) of finely powdered **5** was stirred under $N_2$ for 3 hr. The reaction mixture was decomposed with cold, saturated $NH_4Cl$ solution and the solvent removed *in vacuo*. Inorganic salts were removed by dissolving the residue in MeCN and filtering. The MeCN was removed and the resultant brown oil refluxed with 5% MeOH–KOH for 6 hr. The MeOH was removed, the residue taken up in $H_2O$ and then extracted with EtOAc. The alkaline extract was acidified (HCl), extracted several times with EtOAc, and the solvent removed *in vacuo*. The resultant oil was extracted several times with aq $NaHCO_3$, acidified (HCl), extracted (EtOAc), and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield 0.053 g (67%) of (−)-atrolactic acid. Recrystallization (cyclohexane) afforded atrolactic acid, mp 87–90°, $[\alpha]D$ −14.4° (*c* 1.29, 1 *N* NaOH), corresponding to 25.2% optical purity.[24]

**Apparent Dissociation Constants.**—Approximately 0.02 mol of the HCl salts was dissolved in analytical grade MeOH (5 ml) and titrated against aq 0.115 *N* NaOH. The titration curves were recorded using a Radiometer automatic titrator Model TTT-1, outfitted with an autoburette and recorded (Radiometer-Copenhagen, the London Co., Westlake, Ohio). The titrations were carried out at 23° under constant conditions and the average values of 3 determinations are recorded in Table II.

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(23) 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 337B spectrophotometer, and high resolution ir spectra were obtained on a Perkin-Elmer 521 spectrophotometer. Optical rotations were obtained on a Perkin-Elmer 114 polarimeter with a 1-dm cell.

(24) A. McKenzie and C. Clough, *J. Chem. Soc.*, **97**, 1916 (1910).

# Homologs of Benzomorphan Derivatives. I

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9-Hydroxy-3,7-dimethyl-1,2,4,5,6,7-hexahydro-2,7-methano-3*H*-3-benzazonine (XIX) and its 12-methyl derivatives (XV and XVI) were synthesized and tested for analgetic activity.

Seven-membered homologs of some piperidine derivatives are known to have analgetic activity.[1] Generally, they have weaker analgetic activity and fewer side effects than the corresponding piperidine derivatives. Since the benzomorphan derivatives have been extensively explored as analgetics, and no reports have appeared on their homologs, we undertook the study on 7-membered homologs of benzomorphan derivatives.

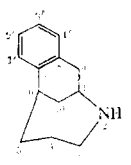
The synthesis of 9-methoxy-12-hydroxy-3,7,12-trimethyl-1,2,4,5,6,7-hexahydro-2,7-methano-3*H*-3-benzazonine (VII)[2] followed the procedure employed in the benzomorphan series[3] (Scheme I). Thus, 3,4-dihydro-1-(3-dimethylaminopropyl)-7-methoxy-1-methyl-2(1*H*)-naphthalenone (II), prepared from I and 3-dimethylaminopropyl chloride, was brominated to give the bromo ketone III hydrobromide. Cyclization of III·HBr with $NH_4OH$ gave the keto methobromide IV in up to 40% yield. The elimination product V accompanied this reaction and gave II on catalytic hydrogenation. Reaction of IV with MeMgI afforded the methylcarbinol derivative VI. Upon pyrolysis, VI gave the tertiary base VII together with the phenolic derivative VIII, which was methylated ($CH_2N_2$) to give VII.

The OH group of VII was assigned the β configuration on the basis of its ir spectrum. A strong band due to an intramolecular OH---N bonding was observed at 3340 $cm^{-1}$. (0.03 and 0.003 mol concd in $CCl_4$). An unexpected difficulty arose, however, when dehydration of VII to the 10-methylene derivative IX was attempted following the procedure successfully used for the benzomorphan analog.[4] $SOCl_2$, $POCl_3$, and TsCl in the presence of pyridine failed to give IX. When treated with $SOCl_2$ in the absence of pyridine, VII gave a very small amount of IX. Pyrolysis of the acetoxy derivative X also gave IX in an unsatisfactory yield.

It was probable that the 10α-hydroxy isomer of VII would be more easily dehydrated than VII. However, the reaction of XI, obtained by pyrolysis of IV, with MeLi gave a product identical with VII,[5] and the 10α-hydroxy isomer was not available for dehydra-

(1) For instance, refer to the article by R. A. Hardy, Jr., and M. G. Howell in "Analgetics," G. deStevens, Ed., Academic Press, New York and London, 1965, p 206.

(2) For convenience, the term "homobenzomorphan" will be given to this series of derivatives in general. Numbering is analogous to that used for benzomorphan.



(3) (a) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960); (b) E. L. May and H. Kugita, *ibid.*, **26**, 188 (1961).

(4) (a) S. Saito and E. L. May, *ibid.*, **27**, 1087 (1962); (b) H. Kugita and M. Takeda, *Chem. Pharm. Bull. (Tokyo)*, **12**, 1163 (1964).

(5) This result constitutes a major deviation from the benzomorphan series. In the latter, the reaction gives stereospecifically the α-OH derivative. See ref 3b.