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Crystal Structures of Analgesics. Hydrochlorides of (−)-Isomethadone, α-Methadol, and α-Methadyl Acetate

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The structures of the hydrochlorides of (−)-isomethadone, α-methadol, and α-methadyl acetate were determined by single-crystal X-ray diffraction methods. The conformation of isomethadone was found to be quite similar to that of methadone hydrobromide. In general, a lack of conformational similarity was observed among those potent acyclic analgesics compared.

The acyclic narcotic analgesics, of which methadone is the most prominent, have structures which permit a certain degree of conformational freedom. Their flexibility has made it difficult for investigators to derive definitive structure–activity relationships for them.[1,2] There have been a number of conformational studies on this class of analgesics in an attempt to pin down the nature of the active conformer.[3-5] In general, the results of such studies are inconclusive and tend to raise many questions.

Though crystal structure analyses of flexible molecules do not necessarily lead to definitive information about their conformations in solution or at the receptor site, they can provide valuable clues. With this in mind, a series of X-ray studies was initiated on a variety of acyclic analgesics, with the hope of finding some loci of commonality between the molecules, which might be responsible for their activity. Such studies are also useful in clarifying structural information derived from spectral and other measurements made on solutions of these compounds.

X-Ray single-crystal analyses of α-methadol hydrochloride (1), α-acetylmethadol hydrochloride (2), and (−)-isomethadone hydrochloride (3) were completed. The three molecules as seen in their crystal structures are shown in Figures 1–3. For convenience in making comparisons, all molecules are drawn and labeled in an analogous manner.

The difference in analgesic potency between the enantiomers of each compound is in most instances quite large. In the present discussion of the data derived from the X-ray studies, reference will only be made to the more potent stereoisomer of each compound.

Discussion

In general, the bond distances and angles in the three structures have values which were expected. The only portion of these molecules where bond distances and angles deviate significantly from their standard values is at C(4). The bonding parameters about C(4) are presented in Figure 4. The nonbonded interactions[6] in this crowded portion of the molecules are the principle reason for the distortions from ideal geometry.

In each of the structures there is an intermolecular bond between the chlorine atom and the proton on the nitrogen. This type of hydrogen bond is observed in crystals of other analgesics[7,8] and ammonium halide compounds. The parameters associated with these bonds are given in Table I.

The hydroxyl proton in 1 also participates in a hydrogen bond with the chloride ion. In this structure the nitrogen proton lies fairly close to O(1), 2.63 (3) Å, noted as a dashed line in Figure 2. This could be construed as a very weak hydrogen bond. Portoghese and Williams[9] proposed such an intramolecular hydrogen bond on the basis of pK_a measurements. There is little doubt that the hydrogen bonding network plays a dominant role in stabilizing the observed conformation of this molecule.

The waters molecules in isomethadone are involved in hydrogen bonds with the halogen and not the molecule.

The principle conformational parameters for the three structures studied are compared to those of methadone hydrobromide[7] (4), methadone base,[10] and (+)-*N*-[(2-benzylmethylamino)propyl]propionanilide hydrobromide[8] (5) in Table II. The latter three molecules are shown in Figures 5–7.

The more potent enantiomers of 4 and 3, as might be expected, have conformations that are very similar. The only conformational difference of major significance between these molecules resides in the spatial orientation of the *N*-methyl groups. To a certain extent this results from the difference in their crystal packing arrangements. The conformation of 3 predicted by Portoghese and coworkers[3-5] is consistent with that found in the crystal. However, their measurements suggest a different conformation for 4, one which is stabilized by an intramolecular N^+–H···O(1) hydrogen bond.

A scrutiny of the tabulated conformational parameters for the acyclic analgesics listed indicates a lack of stereochemical similarity between them. The backbone structure and the orientation of various groups attached to it differ substantially among the compounds. Such was to be expected in light of previous studies on acyclic analgesics which suggest the possibility of multiple binding modes at the receptor or the potential that a number of analgesic receptors exist.[1,2]

There are some spatial parameters which are similiar in the various molecules. The distance between the phenyl rings (given in the table as the distance between the cen-

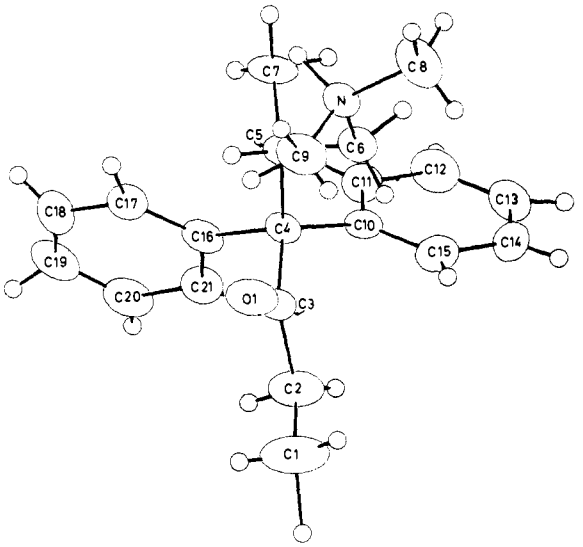

Figure 1. Isomethadone hydrochloride (5*S*, **3**).

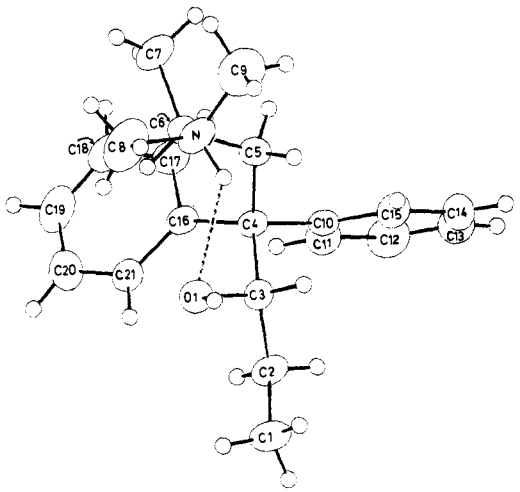

Figure 2. α-Methadol hydrochloride (3*S*,6*S*, **1**).

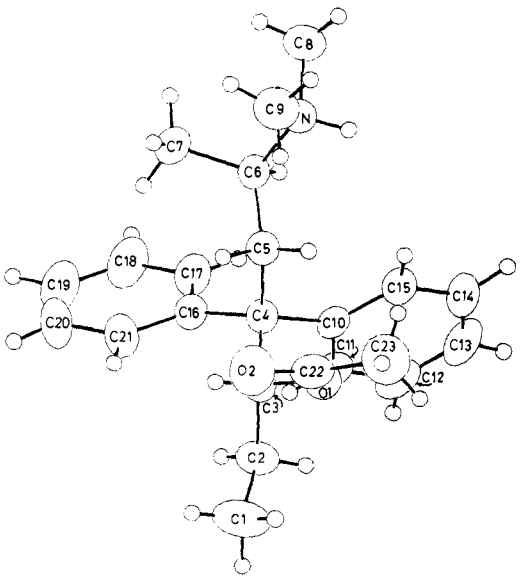

Figure 3. α-Acetylmethadol hydrochloride (3*R*,6*R*, **2**).

troids of the two rings) and the dihedral angle between them is similar in each case with the exception of methadone (base form). The nitrogen does not lie equidistant

Table I. Intermolecular Hydrogen Bonds

Compd	Bond	Distance, Å	Bond	Distance, Å
1	N···Cl⁻	3.153 (2)	(H···Cl⁻)	2.30 (3)
	O(1)···Cl⁻	3.080 (2)	(H···Cl⁻)	2.35 (3)
2	N···Cl⁻	3.008 (2)	(H···Cl⁻)	2.14 (3)
3	N···Cl⁻	3.052 (5)	(H···Cl⁻)	2.10 (6)
	W(1)···Cl⁻	3.18 (2)		
	W(2)···Cl⁻	3.28 (2)		

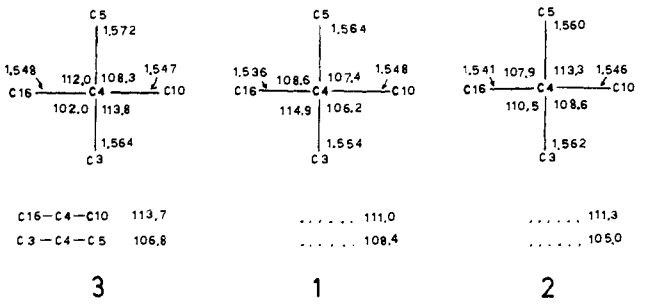

Figure 4. Bond distances and angles about C(4). Estimated standard deviations in bond distances and angles for the three structures are 0.008 Å and 0.5° in **3** and 0.004 Å and 0.3° in **1** and **2**.

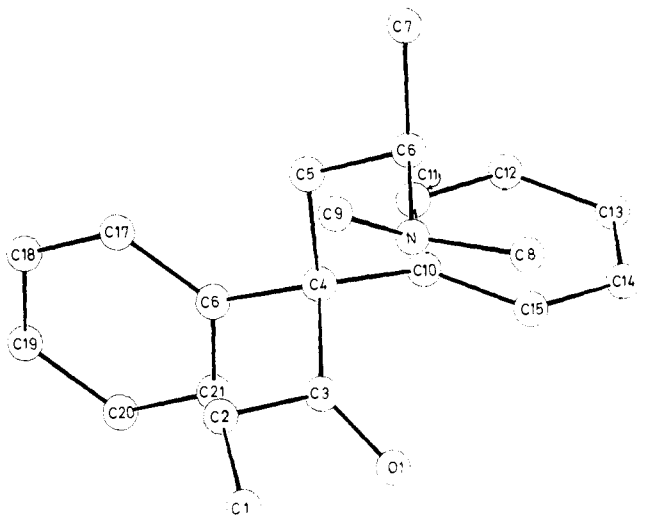

Figure 5. Methadone (base, 6*R*).

from the two phenyl rings but shows an asymmetric relationship. In all but one case [α-methadol hydrochloride (3*S*,6*S*)], it is closer to the phenyl ring (distance to centroid of ring) on the right-hand side of the molecule as illustrated in the figures. The length between the nitrogen and the oxygen on O(3) varies considerably between the compounds listed. In the case where a carbonyl function is present at C(3), the range of $N^{+}\cdots O$ values are much more restricted.

Molecular models† of the compounds indicate that the degree of conformational flexibility in each case is very limited. Only with considerable strain can one distort the molecules from their observed spatial arrangements. A case at point is methadone, where an intramolecular N···C=O interaction in the base is sufficient to stabilize a cyclic conformation, but considerable distortion of the molecular geometry is required. The extent of the distortion suggests that such an interaction is not a very weak one.[10]

†CPK models, Ealing Corp., Cambridge, Mass.

Table II. A Comparison of Torsion Angles (τ) and Some Other Parameters of a Number of Acyclic Analgesics

τ (atoms)	Methadone HBr (6*R*), deg	Isomethadone HCl (5*S*), deg	Methadol HCl (3*S*,6*S*), deg	Methadyl acetate HCl (3*R*,6*R*), deg	Methadone (base, 6*R*), deg	(+)-*N*-[(2-Benzylmethylamino)propyl]propionanilide HBr (6*R*), deg
			Torsion Angles, Degrees			
C(1)-C(2)-C(3)-C(4)	156.7	175.9	−176.5	−170.7	−165.1	178.8
C(2)-C(3)-C(4)-C(5)	−174.1	−167.4	−170.5	−179.4	58.5	174.7
C(3)-C(4)-C(5)-C(6)	76.4	66.2	−77.5	−170.7	65.8	118.4
C(4)-C(5)-C(6)-N	−146.3	−152.5	116.1	−146.2	−79.8	−54.0
C(5)-C(6)-N-C(8)	75.2	−154.6	−158.2	170.5	152.5	168.1
C(5)-C(6)-N-C(9)	−52.9	81.1	75.5	−61.0	−81.0	−69.7
C(1)-C(2)-C(3)-O	−29.0	−10.7	−49.7	68.5	23.8	−2.6
O-C(3)-C(4)-C(5)	11.9	19.2	61.4	−55.6	−130.6	−3.9
C(2)-C(3)-C(4)-C(10)	−50.8	−47.9	−55.4	−57.0	−179.4	
C(2)-C(3)-C(4)-C(16)	70.8	75.0	67.8	64.4	−60.6	6.3
C(3)-C(4)-C(10)-C(15)	−28.0	−33.0	−67.1	−96.9	−29.9	−77.4
C(3)-C(4)-C(16)-C(17)	82.7	89.1	178.8	−156.0	114.9	
C(5)-C(4)-C(10)-C(15)	96.7	85.6	48.8	19.4	94.0	113.9
C(5)-C(4)-C(16)-C(17)	−34.0	−24.7	57.1	89.7	−4.3	
C(4)-C(5)-C(6)-C(7)	98.0		−120.1	91.2	163.7	177.8
C(3)-C(4)-C(5)-C(7)		−171.3				
			Other Parameters			
Ph···Ph distance, Å	5.02	4.98	4.92	4.88	4.81	4.89
Ph···Ph dihedral angle, deg	63.7	62.5	65.0	67.2	80.7	65.3
d[(N···O(1)]	3.81	3.69	3.15	4.88 (5.34)[a]	3.43	3.73
d(N···Ph, right)	5.33	5.36	6.14	5.21	4.81	4.84
d(N···Ph, left)	6.28	6.30	5.34	5.40	5.85	

[a] Distance to O(2) in parentheses.

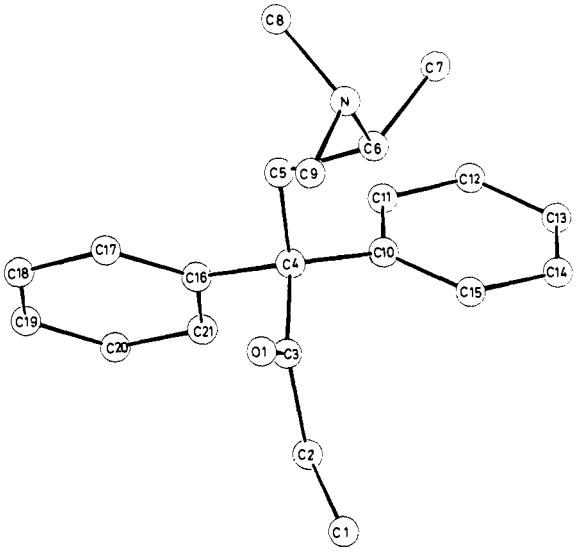

Figure 6. Methadone hydrobromide (6*R*).

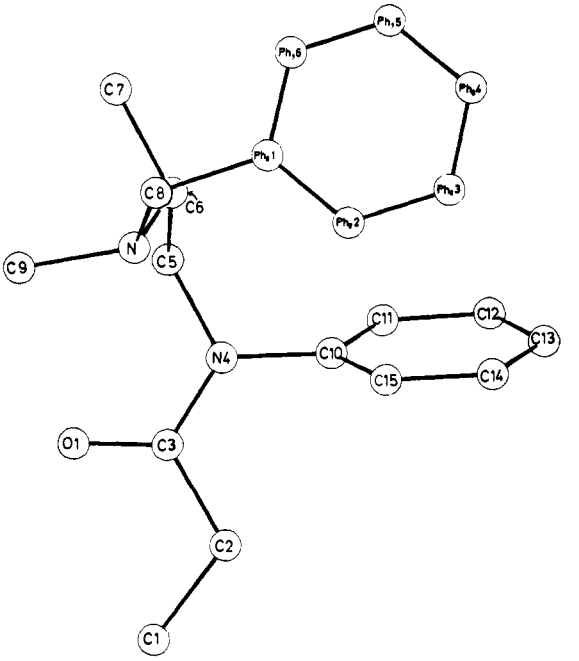

Figure 7. *N*-[(2-Benzylmethylamino)propyl]propionanilide hydrobromide (6*R*).

Experimental Section

Crystals of the three compounds were kindly supplied by Dr. Philip S. Portoghese. Some pertinent crystallographic data for these materials are listed in Table III.

The intensity data for the three compounds were collected by the stationary counter-stationary crystal technique using filtered Cu Kα radiation with balanced filters. The range of data collection was from 0 to 120° in 2θ. Corrections were applied to the data for α_1-α_2 splitting, Lorentz-polarization effects, and absorption. The structures were solved by Patterson and Fourier techniques (heavy atom method) and refined by block-diagonal least squares.

The absolute configuration of isomethadone was determined during the final stages of refinement by making use of the anomalous scattering of chlorine. The reliability factor (*R* value) of the 5*S* configuration was significantly lower than that for the 5*R* antipode. This observation is in accord with the chemically determined chirality of the molecule.[11]

The water molecules in the isomethadone structure were found to reside in crystallographic special positions, along the twofold axes at (0, 0, *Z*) and (0, 0.5, *Z*). This accounts for the excellent agreement between the measured density and that calculated for a monohydrate.

With the exception of the protons on the waters in the 3 structure, all atoms were located and refined. Their positional and thermal parameters are presented in Tables IV and V of the microfilm edition of the journal. (See paragraph at end of paper regarding supplementary material.) A comparison of the measured

Table III

	1	2	3
Solvent	EtOAc	EtOAc	EtOH–Et_2O
a, Å	7.735 (1)	8.060 (1)	11.662 (2)
b, Å	12.068 (1)	15.011 (1)	13.265 (3)
c, Å	21.484 (3)	18.611 (2)	13.048
β, deg	104.52 (1)	99.42 (1)	90.0
Sp gr	$P2_1/c$	$P2_1/c$	$P2_12_12$
d (measd), g/cm³	1.181	1.166	1.195
d (calcd), g/cm³	1.190	1.166	1.197[a]
Z	4	4	4
R value (final)	0.038	0.046	0.074

[a] As monohydrate.

and calculated structure factors is available from the author on request.

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Supplementary Material Available. Tables IV and V will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-1037.

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In Pursuit of Analgetic Agents. Hydro-1,3-ethanoindeno[2,1-*c*]pyridines and Homologs

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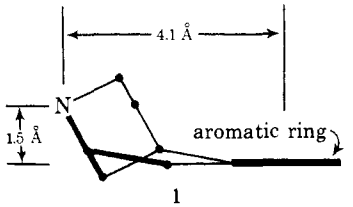
A study was made of the analgesic activity associated with a modified skeletal support for the nitrogen atom and the aromatic ring of the benzomorphans. The compounds involved were 1,2,3,4,4a,9a-hexahydro-9*H*-1,3-ethanoindeno[2,1-c]pyridines of general structure **2** with various substituents on N, C-9, and the aromatic ring. Also included were some "middle ring homologs" which belong to the chemical category of 1,3-ethanobenz[*g*]isoquinolines. These compounds showed activity in preventing the abdominal constriction response in mice induced by acetylcholine and phenyl-*p*-quinone. They were inactive in the D'Amour–Smith "tail flick" test. The three most promising compounds failed to block the intraarterial bradykinin-evoked pain response in the rat. Selected compounds, evaluated as local anesthetics, showed activity in the procaine–cocaine range. Removal of the ethano bridge present in these compounds had no significant effect on the level of activity observed in this series.

The benzomorphan class of analgesics is characterized by the presence of a basic nitrogen atom rather rigidly held about 1.5 Å above the plane of an aromatic ring and displaced about 4.1 Å from the center of that ring (see **1**). A new series of polycyclic bases, the recently described ethanoindeno[2,1-*c*]pyridines,[1] exemplified by structure **2**, has a nitrogen atom suspended about 1.8 Å above the plane of the aromatic ring and displaced about 4.4 Å from the center of this ring. It was therefore of considerable interest to determine the degree of analgesic activity associated with these modified dimensions and a modified supporting skeleton.



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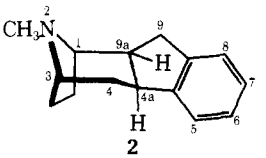

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The present paper describes the preparation of a variety of substituted hydro-1,3-ethanoindeno[2,1-*c*]pyridines, some homologous compounds with the "center" ring enlarged, and a parallel series with the ethano bridge absent.† Structure–activity relationships have been investigated through measurement of prevention of the abdominal constriction response in mice induced by acetylcholine (ACh) and phenyl-*p*-quinone (PPQ). Also used were the D'Amour–Smith tests for narcotic analgesia and narcotic antagonism. Blockade of bradykinin-induced asymmetric motion was the most definitive test employed for nonnarcotic analgesia. Limited data are furnished on toxicity and local anesthetic activity. Biological activity is reported here for 11 indenopyridines described chemically in ref 1.

Chemistry. The general procedure for preparing hexahydro-1,3-ethanoindeno[2,1-*c*]pyridines[1] is shown in eq 1. The mixture of 2α and 2β esters represented by formula **3** was formed by Grignard 1,4 addition to an α,β-unsaturated ester precursor[3] and can be used without separation

† Phenindamine, an antihistaminic agent, is a 9-phenyltetrahydro-1*H*-indeno[2,1-*c*]pyridine. Augstein, *et al.*,[2] report studies on the antidepressant properties of a series of 9-phenylhexahydro-1*H*-indeno[2,1-*c*]pyridines and 5-phenylhexahydro-2*H*-indeno[1,2-*c*]pyridines.