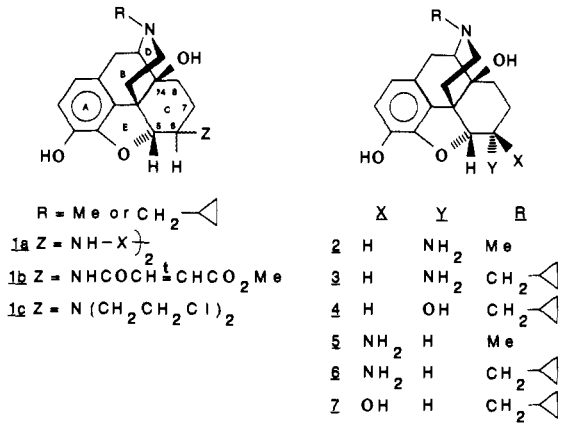
Opioid Receptor Interactions and Conformations of the 6α and 6β Epimers of Oxymorphamine. Solid-State Conformation of 6α-Oxymorphamine

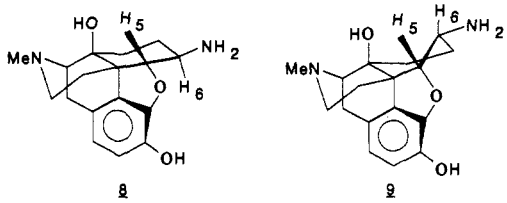
O. William Lever, Jr.,*[†§] Ashok V. Bhatia,[†] and Kwen-Jen Chang[‡]

Departments of Organic Chemistry and Molecular Biology, Wellcome Research Laboratories, Burroughs Wellcome Company, Research Triangle Park, North Carolina 27709. *Received October 29, 1984*

The affinities of the oxymorphamine epimers for μ and δ opioid receptors were determined in vitro. The 6α and 6β epimers are potent μ-selective ligands with similar receptor-binding profiles. The relatively undramatic effect of C-6 chirality on receptor interactions is intriguing in view of the recently demonstrated profound influence of C-6 chirality on ring-C solution conformations (ring C is a chair conformer in the β epimer but adopts a twist-boat conformation in the α epimer) and prompted the determination of the crystal structure of α-oxymorphamine. The crystal structure showed that ring C in this epimer also adopts a twist-boat conformation in the solid state. Molecular modeling of the oxymorphamines in the preferred ring-C conformations (α = boat, β = chair) demonstrated that the 6-amino groups project to spatial loci significantly more proximal (0.35 Å) than would be the case (2.2 Å) if both epimers adopted chair conformations for ring C. Consequently, although the epimeric oxymorphamines differ in ring-C conformation, the principle potential heteroatomic binding sites in each epimer are oriented similarly, which may be partly responsible for the lack of dramatic differences in receptor binding profiles.

Opioid receptors and opioid ligands are the focus of intensive current study.[1] Among the ligands of current interest are a variety of 17-alkyl-4,5a-epoxy-3,14-dihydroxymorphinans with functionalized amino groups at C-6 (cf. **1**), including dimeric ligands,[1] in which two opioids are covalently bridged through their respective 6-amino groups (cf. **1a**), and affinity labels (e.g., **1b**, **1c**),[2] in which a 6-amino substituent is linked to an electrophilic moiety that may alkylate opioid receptors. These ligands typically are derivatives of the parent 6α (**2**) and 6β (**5**) epimers of oxymorphamine or of the 6α (**3**) and 6β (**6**) epimers of naltrexamine. Accordingly, knowledge of the conformational preferences of these 6-amino epimers is important for consideration of ligand–receptor interactions of their derivatives and for exploration of possible relationships between C-6 chirality, conformation, and biological activity. Recent studies have demonstrated that C-6 chirality is an important determinant of the receptor-alkylating profile of certain of the affinity labels derived from the epimeric naltrexamines[3] and that the chirality at C-6 also dramatically influences the ring C conformation of the oxymorphamines in solution.[4] These links between C-6 chirality and biological activity and between C-6 chirality and conformation in 6-amino derivatives of 14-hydroxy-4,5a-epoxymorphinans prompted us to extend our conformational studies[4] to include the crystal structure of 6α-oxymorphamine and to define the opioid receptor-binding properties of the epimeric oxymorphamines.





Receptor Binding of the Oxymorphamines. The affinities of the oxymorphamines[5] for μ and δ opioid receptors were determined in vitro in a rat brain membrane preparation with ^{125}I-Tyr-D-Ala-Gly-NMePhe-Met(O)-ol (0.2 nM) as the μ ligand and ^{125}I-labeled D-Ala^2-Leu^5-enkephalin (0.2 nM) as the δ ligand.[6] The binding affinities in Table I are expressed as IC_{50} values, the concentration that inhibits specific binding by 50%. The binding data show that 6α- and 6β-oxymorphamines are potent μ-selective ligands with affinities for μ receptors that are 19-fold and 12-fold greater, respectively, than their affinities for δ receptors. For each receptor subtype, the epimers differ by less than threefold in their binding affinities, with the β epimer emerging as slightly more potent than the α epimer in binding to each receptor. These differences in receptor-binding profiles are small and suggest that the configuration of the C-6 amino group has a relatively undramatic effect on receptor interactions of the oxymorphamines.

Conformational Considerations. We recently reported that the configuration of the 6-amino group has a profound influence on solution conformations of ring C in the oxymorphamines.[4] High-field nuclear magnetic resonance (NMR) analysis of the epimers demonstrated that the β-epimer **5** adopts a chair conformation for ring C (cf. **8**) and that ring C in the α-epimer **2** exists in a twist-boat conformation (cf. **9**). These preferred conformations were observed for the free bases and for the dihydrochlorides,

[†] Department of Organic Chemistry.
[‡] Department of Molecular Biology.
[§] Present address: Division of Medicinal Chemistry, Ortho Pharmaceutical Corp., Raritan, NJ 08869.

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Table I. Opioid Receptor Affinities of the Oxymorphamines[a]

epimer	receptor binding, I_{50} (nM) ± SEM	
	μ[b]	δ[c]
α (**2**)	13 ± 3	250 ± 75
β (**5**)	9 ± 2	110 ± 50

[a] The assays were performed on the dihydrochlorides and were carried out as previously described (ref 6). [b] Nanomolar concentration that inhibits by 50% the specific binding of ^{125}I-Tyr-D-Ala-Gly-NMePhe-Met(O)-ol. [c] Nanomolar concentration that inhibits by 50% the specific binding of ^{125}I-labeled D-Ala^2-D-Leu^5-enkephalin.

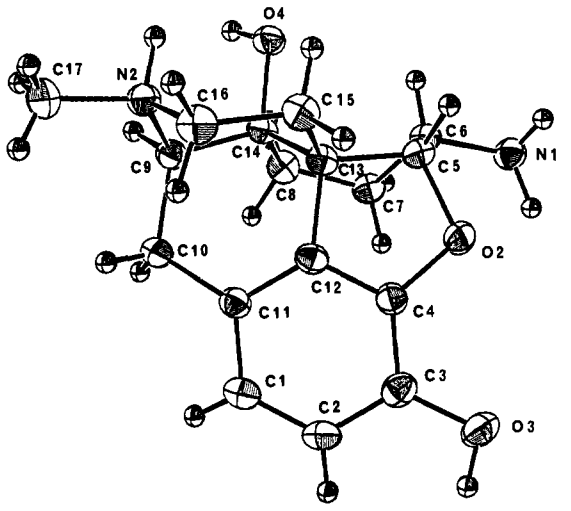

Figure 1. Molecular structure of α-oxymorphamine (2·2HCl·H_2O) showing 30% probability ellipsoids as determined by X-ray crystallography. Chloride ions and water of hydration are omitted for clarity.

and we noted[4] that the boat conformation for the α epimer was unexpected on the basis of previously reported conformational assignments for the closely related 6-hydroxy compounds, the naltrexol epimers **4** and **7**, which were considered more consistent with a chair conformation for ring C in both epimers. We have subsequently examined pairs of epimeric 6-hydroxy compounds, e.g., the 6α (**4**) and 6β (**7**) naltrexols, using high-field NMR techniques. We found that, although 6β-naltrexol (**7**) indeed adopts a chair form for ring C, the actual solution conformation of ring C in the 6α epimer is predominantly a twist-boat,[7] and thus the 6-amino and 6-hydroxy compounds show parallel conformational behavior. These results in solution prompted us to obtain the crystal structure[8] of 6α-oxymorphamine (**2**) to permit a comparison of solution and solid-state conformational preferences.

The molecular structure of 6α-oxymorphamine dihydrochloride monohydrate (2·2HCl·H_2O) as determined by X-ray analysis is shown in Figure 1 and demonstrates that, in the solid state, this epimer adopts a twist-boat conformation for ring C which corresponds to the conformation observed in solution.[4] The molecule has the

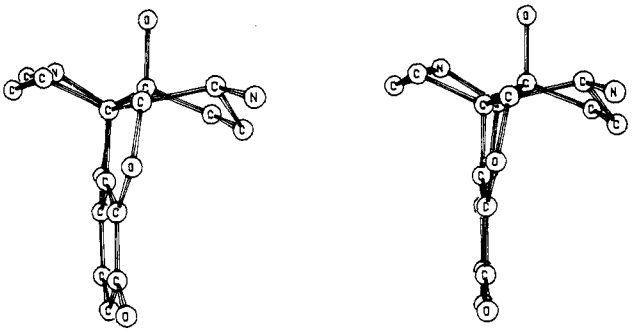

Figure 2. Stereoview of the crystal structure of **2** illustrating the T-shape of the molecule and the chair/boat conformations of rings D/C. Hydrogen atoms, chloride atoms, and water of hydration are omitted for clarity.

characteristic T-shape of the classical opiates, with the piperidine (D) ring and ring C comprising the short arms of the T and the aromatic (A) ring, the oxide (E) ring, and the carbocyclic (B) ring forming the stalk of the T. The T-shape of the classical opiates is often referred to but is rarely depicted graphically, presumably because of the lack of overall conformational perspective usually provided by this view. A stereoview of **2** that illustrates the T-shape of the molecule and that also provides another perspective of the conformational aspects of rings C and D is present in Figure 2.

The representation in Figure 1 shows that the piperidine (D) ring of **2** has a well-defined chair conformation as has been observed in the crystal structures of other pentacyclic opiates. The twist-boat conformation of ring C places the 7α-proton in a position directly over the aromatic ring, which is consistent with the significant NMR shielding effect noted for this proton in the solution studies.[4]

The crystal structure for **2** is especially noteworthy in view of the lack of previously reported cases of 14-hydroxy-4,5a-epoxymorphinans in which a fully saturated C ring adopts a boatlike conformation.[9] Although crystallographic studies of morphine (**10**)[10-12] and codeine (**11**)[13,14] have shown that ring C in these molecules is a boat conformer, this conformational preference has been attributed to the presence of the unsaturated linkage between C-7 and C-8.[15,16] Crystal structures of the 6β-azido compounds **12** and **13** showed that the fully saturated C ring in these 6β-substituted compounds is in a flattened chair form[15,16] and naloxone (**14**)[17,18] and oxymorphone (**15**),[19,20] which have a carbonyl group at C-6, also adopt

(7) These conformational considerations for the 6α-hydroxy epimers appear to apply rigorously only to 4,5a-epoxymorphinans that have a 14-hydroxyl substituent, since the 6α epimers of compounds with a proton at C-14, such as dihydromorphine and dihydrocodeine, adopt a chair conformation for ring C. Crouch, R. C.; Lever, O. W., Jr.; Bhatia, A. V., manuscript in preparation.

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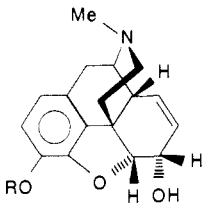
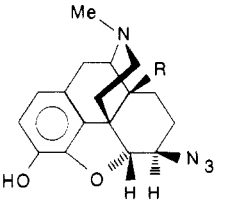
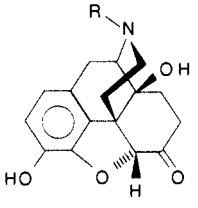
a chair conformation for ring C. A boat form has been observed for the saturated C ring in dihydrometacodeinone (16),[21] but this compound differs distinctly in stereochemistry and pentacyclic framework connectivity from the epoxymorphinanes.



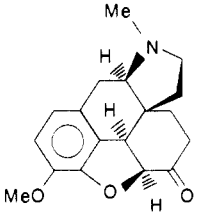
10 R = H
11 R = Me



12 R = OH
13 R = H



14 R = allyl
15 R = Me



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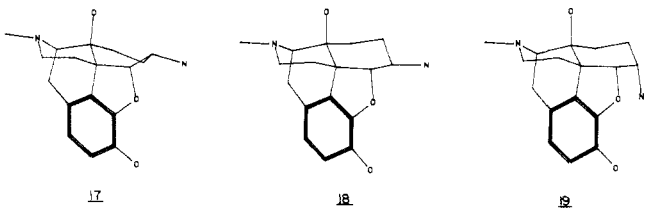
Molecular Modeling of the Oxymorphamines. To probe for a possible link between C-6 chirality, ring C conformation, and receptor interactions, we modeled the epimeric oxymorphamines using the NIH PROPHET system.[22] The X-ray coordinates for **2** (cf. Figure 1 and Table II) provided the model for the α epimer with a ring-C twist-boat (**17**). Approximate models for the β epimer with the chair form for ring C (observed in solution) and for the α epimer with a ring-C chair (not observed by X-ray or NMR) were constructed by manipulation of the crystal structures of **2** and **12**. The β epimer with a ring-C chair (**18**) was modeled from the β-azido compound **12**, which has a ring-C chair, by deleting the 6-azido group, replacing it with a 6-amino group, and adjusting the C-5/C-6, C-6/C-7, and C-6/N bond lengths to correspond to those from the crystal structure of **2**. The α epimer in its disfavored ring-C chair form (**19**) was then constructed from the β model by inverting the C-6 configuration. Although these latter two models are clearly of limited precision,[20] they nonetheless provide approximate molecular structures for qualitative comparisons.



17 18 19

The three models were then matched in pairs by using the recently developed MATCHMOL program.[23] Closest matching of the tertiary nitrogen, the oxygen of the 14-hydroxy group, the phenolic oxygen, and the ether oxygen was performed for each pair, and after the best fit of the matched heteroatoms was computed, the distance between the nitrogen atoms bonded to C-6 was then calculated for each pair. Matching the epimeric oxymorphamines in their preferred ring-C conformations (**17**, α = boat; **18**, β = chair) indicated that the nitrogen atoms of the 6-amino groups project to spatial loci that are significantly more proximal (computed N_α–N_β distance in the **17**/**18** matched pair = 0.35 Å; cf. Figure 3 for a stereoview of this match) than would be the case if both epimers, rather than only the β epimer, adopted chair conformations for ring C (computed N_α–N_β distance in the **18**/**19** matched pair = 2.2 Å). The difference in the projection of the 6-amino groups for the α epimer in its observed boat conformer **17** compared with its disfavored chair conformer **19**, i.e., the N_α-boat–N_α-chair distance in the **17**/**19** match, was computed to be 2.1 Å.

Table II. Fractional Atomic Coordinates and Estimated Standard Deviations for Crystal Structure of 2·2HCl·H_2O

atom	x	y	z
Cl 1	−0.1905 (1)	−0.9160 (0)	−0.14848 (9)
Cl 2	−0.9723 (1)	−0.7606 (1)	−0.45619 (9)
O1 (H_2O)	−0.1817 (5)	−0.4385 (4)	−0.7810 (3)
O2	−0.2519 (3)	−0.9373 (2)	−0.6865 (2)
O3	−0.1920 (3)	−0.6848 (3)	−0.7515 (3)
O4	−0.6662 (3)	−1.1936 (2)	−0.6159 (2)
N1	−0.1831 (4)	−1.0145 (3)	−0.4367 (3)
N2	−0.8407 (4)	−1.1328 (3)	−0.8416 (3)
C1	−0.6600 (5)	−0.7211 (3)	−0.8152 (3)
C2	−0.4988 (5)	−0.6683 (4)	−0.8044 (3)
C3	−0.3514 (4)	−0.7348 (4)	−0.7652 (3)
C4	−0.3737 (4)	−0.8569 (3)	−0.7395 (3)
C5	−0.3435 (4)	−1.0450 (3)	−0.6478 (3)
C6	−0.3562 (4)	−1.0441 (3)	−0.5030 (3)
C7	−0.4889 (5)	−0.9539 (4)	0.4658 (3)
C8	−0.6678 (4)	−0.9898 (4)	−0.5225 (3)
C9	−0.8349 (4)	−1.0395 (3)	−0.7355 (3)
C10	−0.8505 (4)	−0.9073 (3)	−0.7858 (3)
C11	−0.6803 (4)	−0.8454 (3)	−0.7915 (3)
C12	−0.5326 (4)	−0.9091 (3)	−0.7590 (3)
C13	−0.5212 (4)	−1.0410 (3)	−0.7227 (3)
C14	−0.6720 (4)	−1.0660 (3)	−0.6460 (3)
C15	−0.5272 (4)	−1.1238 (4)	−0.8417 (3)
C16	−0.6975 (5)	−1.1151 (4)	−0.9237 (3)
C17	−1.0083 (5)	−1.1393 (4)	−0.9192 (4)
H1	−0.757 (6)	−0.685 (6)	−0.832 (5)
H2	−0.481 (6)	−0.593 (6)	−0.824 (5)
H5	−0.278 (4)	−1.119 (4)	−0.678 (3)
H6	−0.383 (4)	−1.126 (4)	−0.479 (3)
H7α	−0.453 (5)	−0.874 (5)	−0.492 (4)
H7β	−0.473 (4)	−0.947 (4)	−0.371 (3)
H8α	−0.737 (5)	−0.913 (5)	−0.538 (4)
H8β	−0.723 (5)	−1.052 (5)	−0.460 (4)
H9	−0.944 (4)	−1.062 (4)	−0.684 (3)
H10α	−0.920 (5)	−0.860 (5)	−0.723 (4)
H10β	−0.917 (5)	−0.910 (4)	−0.873 (4)
H15α	−0.432 (4)	−1.102 (4)	−0.895 (3)
H15β	−0.515 (5)	−1.205 (5)	−0.812 (4)
H16α	−0.724 (4)	−1.036 (4)	−0.961 (3)
H16β	−0.714 (5)	−1.176 (5)	−0.987 (4)
H(C17)	−1.090 (5)	−1.153 (5)	−0.867 (4)
H(C17)	−1.001 (7)	−1.190 (6)	−0.976 (5)
H(C17)	−1.036 (7)	−1.079 (7)	−0.968 (5)
H(O1) (H_2O)	−0.155 (9)	−0.382 (9)	−0.712 (7)
H(O1) (H_2O)	−0.076 (7)	−0.438 (7)	−0.810 (6)
H(O3)	−0.211 (6)	−0.608 (7)	−0.774 (5)
H(O4)	−0.762 (5)	−1.203 (5)	−0.577 (4)
H(N1)	−0.114 (6)	−1.073 (5)	−0.454 (4)
H(N1)	−0.193 (7)	−0.991 (6)	−0.355 (5)
H(N1)	−0.131 (5)	−0.941 (5)	−0.470 (4)
H(N2)	−0.836 (5)	−1.213 (5)	−0.797 (4)

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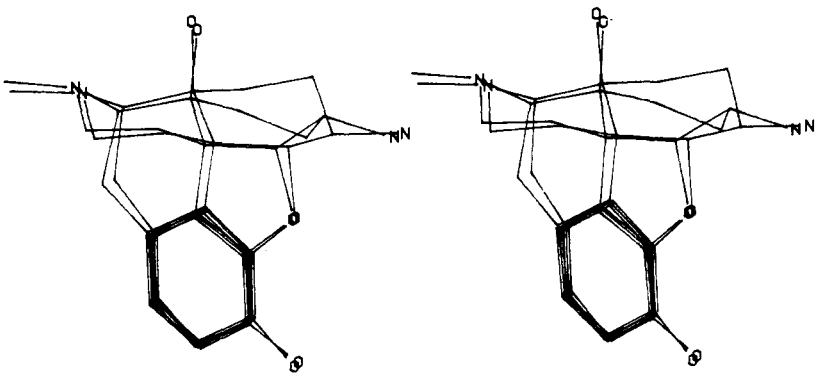

Figure 3. Stereoview of the MATCHMOL-computed matching of the preferred conformations ($\alpha = 17, \beta = 18$) of the epimeric oxymorphamine models.

It is evident from Figure 3 that the epimeric oxymorphamines in their preferred conformations exhibit quite similar spatial orientations for their respective 6-amino groups.

Discussion

Although the precise torsional and stereoelectronic factors that govern the ring-C conformational preferences of the epimeric oxymorphamines (**2** and **5**) and naltrexols (**4** and **7**) have not been delineated by our studies, the crystallographic and solution conformational data demonstrate that the C-6 chirality strongly influences the ring-C conformation in these compounds and furthermore suggest a general guideline for conformational behavior for related 14-hydroxy[7] analogues: for 6-hydroxy or 6-amino derivatives of 14-hydroxy-4,5a-epoxymorphinans in which ring C is saturated, ring C will preferentially adopt a chair conformation when the C-6 substituent is in the β orientation and will preferentially adopt a twist-boat conformation when the C-6 substituent is in the α orientation.

The comparative molecular modeling of the oxymorphamine epimers (Figure 3) illustrates that all of the potential heteroatomic binding sites, including the 6-amino groups, are similarly oriented in each isomer despite the conformational differences of their respective C rings. This provides one possible explanation for the lack of dramatic differences in receptor interactions of these configurational isomers. An alternative explanation could be that the 6-amino functions simply do not interact in a critical manner with the receptor surface during ligand binding. The latter possibility has been suggested to be the case for the naltrexamine epimers, which, just as observed for the oxymorphamines, did not differ greatly in receptor affinity in vitro.[24]

This suggestion may have arisen at least partly from conformational considerations for the naltrexamines[24] that were formulated by analogy with the conformational assignments for the naltrexols that prevailed at that time.[25,26] Thus, the naltrexol epimers were each considered to have chair forms for ring C,[25,26] which implied significantly different positioning (axial vs. equatorial locations) for the epimeric 6-hydroxy groups and, by extrapolation, for the epimeric 6-amino groups of the naltrexamines.[24] Accordingly, the absence of large differences in receptor affinity of the naltrexamine epimers might imply the absence of critical receptor interactions around C-6. However, the possibility that similar receptor affinities might reflect instead a similar positioning of the 6-amino groups in each epimer is suggested by our recent assignment of 6α-naltrexol[7] (and 6α-oxymorphamine)[4] as twist-boat conformers for ring C and by our modeling study (Figure 3). The data presented here do not specifically address this issue, although there is ample literature suggesting that the biological activity of the epoxymorphinan agonists and antagonists is tolerant of a variety of C-6 substituents,[27-30] and it is conceivable that the degree of interaction between the receptor surface and the heteroatom directly bonded to C-6 may indeed by minimal. Our conformational studies, however, do suggest that whatever the extent of this interaction, differences in the C-6 chirality of epimeric 14-hydroxy ligands will be moderated in spatial terms by conformational factors that lead to a similar positioning of the bond from C-6 to the heteroatom.

Provided that these conformational differences are maintained in the receptor-bound state, in cases of extended functionality emanating from C-6, such as the affinity labels derived from the epimeric naltrexamines and oxymorphamines (cf. **1b**, **1c**), observed differences in biological activity may be due to more subtle differences in the positioning of the extended functionality, with respect to the receptor surface, than are implied by the axial/equatorial projections applied previously[2,3] for the C-6 configurational isomers. However, the possibility that receptor-induced conformational changes may occur, or alternatively, that the epimeric ligands may have different binding orientations, cannot be ruled out on the basis of presently available data. In this regard, it is interesting to note that the epimeric 6-hydroxy compounds derived from the antagonists naltrexone and naloxone have in vivo profiles that are dependent upon C-6 chirality: the β epimers are antagonists with reduced potency relative to the 6-keto compounds, and the α epimers display agonist–antagonist behavior.[31]

Experimental Section

Oxymorphamine epimers **2** and **5** were prepared by the published methods.[5] Opioid receptor binding assays were performed as previously described.[6]

Single-Crystal X-ray Analysis of 6α-Oxymorphamine Dihydrochloride Monohydrate (2·2HCl·H_2O).[8] A colorless prismatic crystal of 2·2HCl·H_2O was obtained from acetone–water.

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The crystal had approximate dimensions of 0.25 × 0.20 × 0.10 mm. Preliminary examination and data collection were performed with Cu Kα radiation (λ = 1.541 84 Å) on an Enraf Nonius CAD4 computer-controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 23 reflections in the range $9 < \theta < 26°$, measured by the computer-controlled diagonal-slit method of centering. The monoclinic cell parameters and calculated volume are a = 7.895 (1) Å, b = 11.008 (2) Å, c = 10.501 (1) Å, β = 95.50 (1)°, V = 908.4 Å^3. For Z = 2 and FW = 393.31 the calculated density is 1.44 g/cm^3. The space group was determined to be $P2(1)$. A total of 2068 reflections were collected, of which 1961 were unique and not systematically absent. The structure was solved by direct methods. Hydrogen atoms were located and their positions and isotropic thermal parameters were refined. The structure was refined in full-matrix least squares. Atomic coordinates are listed in Table II.

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Novel Nonnarcotic Analgesics with an Improved Therapeutic Ratio. Structure-Activity Relationships of 8-(Methylthio)- and 8-(Acylthio)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines

Mikio Hori,*† Masatoshi Ban,† Eiji Imai,† Noriyuki Iwata,† Yoshinari Suzuki,† Yutaka Baba,† Tokiko Morita,†,‡ Hajime Fujimura,§ Masakatsu Nozaki,⊥ and Masayuki Niwa⊥

Gifu Pharmaceutical University, 6-1, Mitahora-Higashi 5 Chome, Gifu 502, Kyoto Pharmaceutical University, Yamashina Misasagi Nakauchi, Kyoto 607, and Gifu University School of Medicine, 40 Tsukasa, Gifu 500, Japan.
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Conversion of the 8-phenolic 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines to the corresponding 8-thiophenolic analogues was achieved by three different routes. Diazotization of 8-amino-2,6-methano-3-benzazocine (**2**) followed by the reaction with CH_3SNa afforded 8-(methylthio)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**3**). Another route using Grewe cyclization was also examined for the synthesis of **3**. As the most effective route, Newman-Kwart rearrangement of benzazocines was selected and closely investigated. 8-(*N*,*N*-Dimethylthiocarbamoyl)oxy derivatives (**6a-e**) rearranged to 8-(*N*,*N*-dimethylcarbamoyl)thio derivatives (**7a-e**) in good yields. Reductive cleavage of **7a-e** and subsequent methylation or acylations gave the title compounds (**3**, **8-24**). Although analgesic activities of sulfur-containing benzazocines decreased compared to the corresponding hydroxy compounds, the *N*-methyl derivative (*S*-metazocine, **8**) showed potent analgesic activity.

Recently heterocyclic analogues of 2,6-methano-3-benzazocines, pyridomorphans,[1] thienomorphans,[2] pyrrolomorphans,[3] and thiazolomorphans[4] were reported. However, only limited examples of chemical modifications of the 8-hydroxy group of the skeleton have appeared, e.g. simple alkylation, acylation, or substitution with halogeno groups.[5] Very recently, Wentland et al. reported the synthesis and pharmacology of 8-aminocyclazocines,[6] but no other functionalized benzomorphans at the 8-position have appeared so far.

It has been considered that an interaction between a phenolic group of a narcotic compound with a sterically rigid chemical structure and an opioid receptor binding site is necessary to initiate its biological activity.[7] Therefore, we undertook the synthesis of 8-mercapto-benzomorphans[8] and evaluation of the pharmacological activity with the concept of bioisosterism[9] between oxygen and sulfur.

Chemistry. We accomplished the introduction of sulfur groups by three different routes (A-C). In route A we selected 8-nitro-3,6(e),11(a)-trimethyl-2,6-methano-3-benzazocine (**2**)[10] as the starting material. Reduction of **2** and treatment with $NaNO_2$ in dilute H_2SO_4 solution followed by the reaction with aqueous CH_3SNa afforded 8-methylthio derivative **3** in 49% yield. The *S*-methyl signal appeared at δ 2.47, and the structure of **3** was established by physicochemical data such as mass spectra. Although the introduction of the sulfur group was successful, this method cannot be applied to *N*-aralkyl-2,6-

† Gifu Pharmaceutical University.
‡ Nēe Nagai.
§ Kyoto Pharmaceutical University.
⊥ Gifu University School of Medicine.

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