in ice-cold 0.05 M sodium–potassium phosphate buffer (pH 7.4). After centrifugation at 48000*g* for 20 min (Sorvall RC2-B), the supernatant was discarded, the pellet was resuspended in distilled water, and the process was repeated. The final pellet was resuspended in 50 volumes of ice-cold 0.05 M Tris buffer (pH 7.4). Aliquots of brain tissue (final concentration 1.25 mg/mL), [^{3}H]spiperone (100 pM), and drugs (freshly prepared in distilled water) were incubated in buffer (final assay volume 2 mL) for 30 min at 37 °C. The binding reaction was terminated by filtration in vacuo over Whatman GF/B filters, and radioactivity was extracted overnight in 6 mL of scintillation fluid [1 L of toluene (Baker), 1 L of Triton X-100 (NEN), 169 of Omnifluor (NEN)] and measured in a Searle Mark II liquid scintillation counter (45% efficiency). Specific [^{3}H]spiperone binding was defined as the difference between binding in the absence and in the presence of 1 μM (+)-butaclamol. The negative logarithm of the concentration of drug producing a 50% inhibition of specific binding (pIC_{50}) values were estimated graphically from logarithmic Hill plots and converted to IC_{50} values.

Acknowledgment. We gratefully acknowledge the hospitality given by H. I. Yamamura to one of us (C.J.G.) and thank Marla Bliss for technical assistance in performing the [^{3}H] spiperone binding. Research performed at the University of Arizona was supported, in part, by Grant MH 31184 from the United States Public Health Service.

Stereochemical Studies on Medicinal Agents. 25.[1] Absolute Configuration and Analgetic Potency of β-1,2-Dimethyl-4-phenyl-4-(propionyloxy)piperidine Enantiomers

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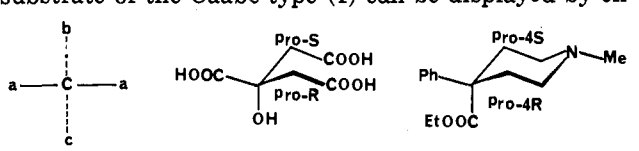
Enantiomers of β-1,2-dimethyl-4-phenyl-4-(propionyloxy)piperidine (4) were employed as probes to demonstrate that opioid receptors are capable of distinguishing between the enantiotopic edges (the Ogston effect) of the piperidine ring. These enantiomers, (−)- and (+)-4·HCl, were prepared by esterification of the corresponding alcohols, (+)- and (−)-**4a**. Single crystal X-ray studies of (−)-**4a**·HCl reveal that it possesses the 2*R*,4*S* absolute configuration. Analgetic testing in mice (hot-plate) and receptor binding studies indicate that (−)-(2*S*,4*R*)-4·HCl is approximately ten times more potent than its enantiomer. The results are consistent with the operation of the Ogston effect in the interaction of achiral 4-phenylpiperidines with opioid receptors. Additionally, it is suggested that the piperidine ring of these and other closely related 4-phenylpiperidines bind within a receptor subsite cleft whose dimensions exclude diequatorial 2,6- and 3,5-dimethyl-substituted ligands.

It is now generally recognized that differentiation of chemically like, paired groups (enantiotopic groups) in a substrate of the Caabc type (1) can be displayed by enzymes.[2] Thus, substrates which contain a plane of symmetry often are found to undergo enzymatic transformation specifically on one of their enantiotopic groups. In his now classical paper, Ogston was the first to point this out in connection with the enzymatic conversion of citrate (2) in the Krebs cycle.[3,4] This type of selectivity is sometimes referred to as the "Ogston effect".[5] Although the Ogston effect can be demonstrated unequivocally in enzyme-catalyzed reactions through radiolabeling experiments, a similar approach cannot be employed to investigate the interaction of ligands with noncatalytic recognition sites.



1 2 3

In an effort to investigate the Ogston effect in the action of narcotic analgetics, we had employed a methyl group to label the enantiotopic edges of the piperidine ring in **3**.[6] The methyl group was selected because it is known that the C-5 and C-6 methyl groups interfere with ligand–receptor association of the less potent enantiomers of methadone and isomethadone, respectively.[7,8] Initially, the C-3 position was the site of attachment of the methyl group to the *pro*-4*R* and *pro*-4*S* enantiotopic edges of **3** in these studies.[6] Later publications discussed related compounds substituted at other centers.[9–14] However, interpretation of the results was complicated by the finding that alkyl substitution vicinal to the C-4 center induced a chiral orientation of the phenyl (Ph) group. In fact, the feature common to all of the analgetically more potent enantiomers is the sign of the torsion angles between the Ph and piperidine ring.[7]

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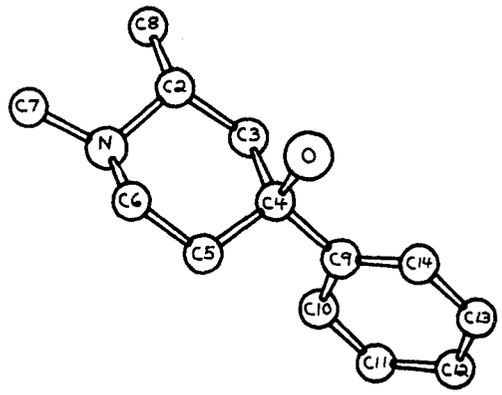
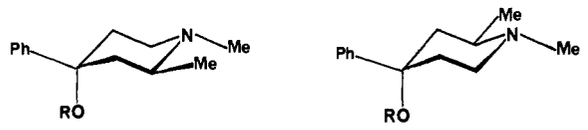


Figure 1. The absolute configuration of (−)-4a·HCl as determined from single crystal X-ray studies.

In this paper we describe our effort to sort out conformational factors from configurational effects through the use of (+)-4 and (−)-4 as receptor probes. These enantiomers were employed because the 2-Me substituent is not expected to induce rotational effects on the equatorial 4-Ph group. Consequently, the receptor enantioselectivity of 4 might reflect the ability of the 2-Me substituent in one of the enantiomers to interfere with ligand–receptor association.



4, R = COC_2H_5
4a, R = H

Chemistry. The preparation of (±)-β-1,2-dimethyl-4-phenyl-4-piperidinol [(±)-4a] was accomplished using the procedure of McErlane and Casy.[15] Optical resolution of the racemate was carried out by fractional crystallization of the diastereomeric salts formed with an equivalent amount of (+)- or (−)-di-*p*-toluoyltartaric acid. Upon treatment with NH_4OH, these salts afforded the corresponding bases, (−)-4a and (+)-4a, respectively. Treatment of each of these enantiomeric alcohols with propionyl chloride in dry toluene produced the corresponding desired esters, (+)-4·HCl and (−)-4·HCl, which were employed in the biological testing.

Single crystal X-ray studies were performed on the alcohol, (−)-4a·HCl, derived from its base, (−)-4a, in order to determine the absolute configuration. The absolute stereochemistry of (−)-4a·HCl was found to be 2*R*,4*S* (Figure 1). This also is the configuration of its free base, (−)-4a, which was converted to the ester (+)-4·HCl. Based on the reasonable assumption that the stereochemical integrity of the chiral centers remain intact during the esterification reaction, the ester derived from (−)-4a is designated as (+)-(2*R*,4*S*)-4·HCl and its enantiomer as (−)-(2*S*,4*R*)-4·HCl.

Pharmacology. The racemic and enantiomeric forms of 4 were evaluated using the hot-plate procedure[16] after sc administration in mice (Table I). Inhibition of the binding of [^{3}H]etorphine to putative opioid receptors in guinea pig brain homogenate was performed by the method of Pert and Snyder[17] as modified by Pasternak et al.[18] It can be noted that (−)-4 is twice as potent as morphine and ten times more potent than its enantiomer. This potency difference between enantiomers is paralleled by binding studies which give an IC_{50} ratio of approximately nine. It is therefore reasonable to assume that receptor-related events are responsible for the enantioselectivity.

Table I. Analgetic Potency and Receptor Binding of β-1,2-Dimethyl-4-phenyl-4-(propionyloxy)piperidine Enantiomers

compd[a]	confign	ED_{50},[b] mg/kg	IC_{50},[d] μM
(−)-4	2*S*,4*R*	0.53 (0.40–0.71)[c]	1.2
(+)-4	2*R*,4*S*	5.5 (3.8–7.8)	11.0
(±)-4		0.52 (0.36–0.74)	2.0
3[e]		1.3 (1.1–1.5)[e]	
morphine		1.2	

[a] Tested as HCl salts of 4 in aqueous solution. The sign rotation is that of the salt. [b] Tested by the hot-plate procedure after sc injection into mice.[16] [c] Confidence interval (95%). [d] The concentration of test agent required to displace 50% of stereospecifically bound [^{3}H]etorphine (2.5 nM) from opioid binding sites in guinea pig brain homogenate. Each value is the mean of three determinations. [e] Reference 6.

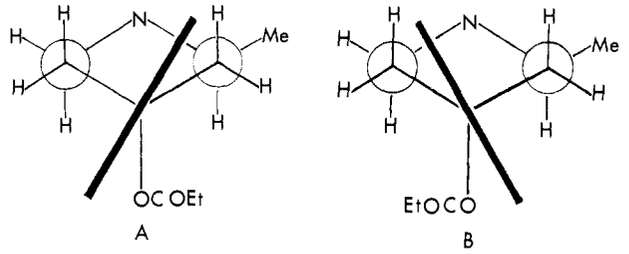
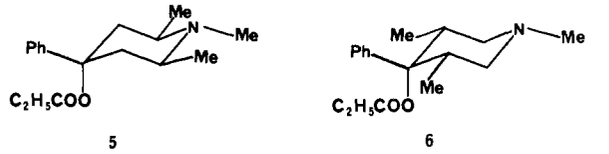


Figure 2. Projection formulas of two Ph rotamers of (−)-(2*S*,4*R*)-4.

Stereostructure–Activity Relationship. Molecular models reveal that the 2-Me substituent of 4 should have little if any influence on the phenyl (Ph) rotamer population when these groups are in the highly favored diequatorial conformation. It is therefore a reasonable assumption that each enantiomer possesses approximately equal populations of Ph rotamers A and B as illustrated by the projection formulas of (−)-4 (Figure 2). This is distinctly different from other prodines that possess alkyl substituents vicinal to the Ph group. In such cases, a gauche alkyl–phenyl interaction induces a skewed Ph rotamer distribution.[7] Consequently, it seems plausible that the greater affinity of (−)-4 for opioid receptors can be attributed to configurational factors rather than to a methyl-induced orientation of the Ph group.

Since the less potent enantiomer (+)-4 is considerably less potent than the demethyl analogue[6] 3, it seems likely that this effect is due to direct intermolecular steric hindrance between the 2-Me of (+)-4 and the receptor. On the other hand, the 2-Me group in the more potent enantiomer (−)-4, being located on the *pro*-4*R* enantiotopic edge, does not adversely affect binding.

Of relevance to the present study are reports that the diequatorial analogues 5 and 6 are devoid of analgetic activity.[19,20] The fact that even high doses of 5 and 6



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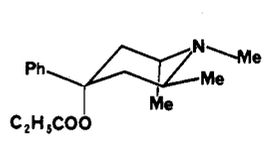
produce no analgesia is in contrast to the less potent enantiomer (+)-4, which is approximately as potent as meperidine. This suggests that opioid receptors contain a cleft whose dimensions exclude a piperidine ring which contains 2,6- or 3,5-diequatorial methyl groups but which is capable of accommodating a single 2-Me group on either enantiotopic edge. Accordingly, there is sufficient play in the binding so that either (+)-4 or (−)-4 can bind within the cleft, with the latter having greater affinity.

Consistent with this view is the fact that the 2,6- and 3,5-dimethyl isomers (±)-7[21] and (±)-8[9] possess activity



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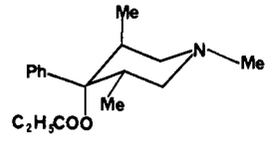

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comparable to the less potent enantiomer (+)-4. Presumably, these compounds are capable of binding within the cleft because the width of molecules that contain an *axial–equatorial* arrangement of methyl groups is less than those that contain a *diequatorial* arrangement (5 and 6).

It is significant that the observed potencies of various stereoisomeric and regioisomeric phenylpiperidines are not simply the sum of the contribution of the individual methyl groups. This suggests that there are sufficient differences in the interaction of these ligands with opioid receptors to affect the binding contributions of individual moieties. Thus, the position of methyl substitution in the phenylpiperidine analgetics to some degree modifies their binding mode to opioid receptors.

In summary, the stereostructure–activity relationship of (+)- and (−)-4 is consistent with the operation of the Ogston effect in the interaction of symmetric 4-phenylpiperidines (e.g., meperidine and 3) with opioid receptors. It appears that the *pro*-4*S* enantiopic edge of the piperidine ring next to the basic nitrogen of 3, in which an equatorial Me substituent interferes with binding, is more intimately involved in the receptor interaction than the corresponding position on the *pro*-4*R* enantiotopic edge. It is suggested that the piperidine ring of these ligands binds within an opioid receptor cleft. Moreover, the width of the cleft excludes ligands beyond a certain width. Finally, the nonadditivity of analgetic potency contributed by methyl substitution on the piperidine ring of 4-phenylpiperidenes is consistent with the mode of interaction of the ligand within the receptor subsite being dependent upon the location of the Me group in the molecule.

Experimental Section

Melting points were determined in open glass capillaries in a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and agree with theoretical values within ±0.4%. Optical rotations were obtained using a Perkin-Elmer 241 MC polarimeter. Liquid scintillation spectrometry was done with a Beckman CPM 100. Infrared and proton NMR spectra on each product were obtained on Perkin-Elmer 251 and JOEL Minimar 100 instruments, respectively. In all cases, spectral data were consistent with the assigned structure.

Optical Resolution of (±)-β-1,2-Dimethyl-4-phenyl-4-piperidinol [(±)-4a]. Racemic **4a** was prepared following the methods described by Casy and McErlane.[15] The β diastereomer employed in the resolution procedure had mp 106–108 °C and δ ($CDCl_3$) 2.3 (1-Me) and 1.07 (2-Me) in agreement with reported values.[15] Racemate **4a** (1.20 g, 5.58 mmol) and (−)-di-*p*-toluoyltartaric acid (2.28 g, 5.88 mmol) were dissolved in 40 mL of MeOH with the aid of heating and stirring. The solution was filtered, the MeOH was removed in vacuo, and the residue was dissolved in 40 mL of hot 2-butanone. The mixture was allowed to stand for 4 h at 23 °C and was filtered to afford 2.0 g of a salt: mp 155–158 °C; $[\alpha]^{23}_D$ −88.1° (*c* 1, MeOH). Two subsequent crystallizations from MeOH gave 1.28 g [mp 156–159 °C; $[\alpha]^{23}_D$ −89.3° (*c* 1, MeOH)] and then 0.86 g of salt [mp 158–159 °C; $[\alpha]^{23}_D$ −92.0° (*c* 1, MeOH)]. Further recrystallizations from MeOH failed to change the $[\alpha]_D$ or mp. Anal. ($C_{33}H_{37}NO_9$) C, H, N.

The resolved salt (0.85 g) was dissolved in H_2O (10 mL) and made basic (pH 11) with NH_4OH. The solution was extracted with $CHCl_3$ (4 × 2 mL), the combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The remaining oil was dissolved in 25 mL of boiling hexane and allowed to stand at room temperature in an unstoppered Erlenmeyer flask. The needle-like crystals which formed were collected by filtration and dried to give 190 mg (35%) of (+)-**4a**: mp 85–87 °C; $[\alpha]^{23}_D$ +34.2° (*c* 1, $CHCl_3$), +20.1° (*c* 1, MeOH).

Ethereal HCl (0.2 mL) solution was added to 70 mg of (+)-**4a** dissolved in 10 mL of anhydrous Et_2O. The solid salt which formed was collected by filtration and immediately dissolved in 8 mL of warm acetone. The flask was stoppered and left to stand at room temperature. The needle-shaped crystals which formed were isolated by filtration and dried in vacuo to yield 57 mg of (+)-**4a**·HCl: mp 198–200 °C; $[\alpha]^{21}_D$ +0.5° (*c* 1, MeOH).

To ensure that isomerization had not occurred in converting (+)-**4a** to its HCl salt, a sample of (+)-**4a**·HCl was converted back to the free base and crystallized from hexane. The recovered **4a** had $[\alpha]_D$ of +20.0° (*c* 1, MeOH).

The combined mother liquors from the above resolution were evaporated to dryness, dissolved in H_2O, made basic (NH_4OH), and extracted with 3 × 20 mL of $CHCl_3$. After the extract was dried (Na_2SO_4) the $CHCl_3$ was removed, the oily residue was dissolved in hexane. On standing at room temperature, 0.78 g of partially resolved **4a**, $[\alpha]^{23}_D$ −5.0° (*c* 1, MeOH), was obtained. This was dissolved in 30 mL of MeOH together with 1.53 g of (+)-di-*p*-toluoyltartaric acid. The MeOH was removed in vacuo, and the resulting oil was dissolved in hot 2-butanone. The precipitate that formed was collected by filtration, dissolved in 30 mL of hot MeOH, and then cooled to −10° for 12 h to afford 1.1 g of salt: mp 156–159 °C; $[\alpha]^{23}_D$ +88.8° (*c* 1, MeOH). Recrystallization from 15 mL of MeOH at −10 °C yielded 0.91 g of crystalline material: mp 158–160 °C; $[\alpha]^{23}_D$ +90.0° (*c* 1, MeOH). Two additional recrystallizations did not change the $[\alpha]_D$ or mp. Anal. ($C_{33}H_{37}NO_9$) C, H, N.

The free base (−)-**4a** was obtained by a procedure identical with that described for its enantiomer: yield 0.24 g (40%); mp 85–86 °C; $[\alpha]^{23}_D$ −20.3° (*c* 1, MeOH). The salt, (−)-**4a**·HCl, mp 196–198 °C, was employed in the single crystal X-ray studies.

β-1,2-Dimethyl-4-phenyl-4-(propionyloxy)piperidine Hydrochloride [(−)- and (+)-4·HCl]. Freshly distilled propionyl chloride (0.4 g) was added to 150 mg (0.74 mmol) of (+)-**4a** in dry toluene (10 mL) containing (100 mg) anhydrous $KHCO_3$ and maintained under N_2. The mixture was heated at 90 °C for 12 h and then cooled, and H_2O (2 mL) was added. The organic phase was separated and extracted with aqueous $NaHCO_3$ solution (2 × 2 mL), and the toluene was removed in vacuo. Dissolution of the residue in a small volume of hexane and addition of several drops of ethereal HCl resulted in the formation of a semisolid. The solvent was decanted from this material and washed with hexane (2 × 2 mL). Dissolution of this material in boiling EtOAc (2 mL) and cooling afforded crystalline (−)-4·HCl: yield 80 mg (63%); mp 190–192 °C; $[\alpha]^{23}_D$ −5.6° (*c* 0.5, MeOH). An identical procedure using 150 mg (0.5 mmol) of (−)-**4a** yielded 90 mg (60%) of (+)-4·HCl: mp 192–193 °C; $[\alpha]^{23}_D$ +5.2° (*c* 0.5, MeOH). The racemic alcohol (±)-**4a** (0.6 g, 2.0 mmol) yielded 0.32 g (54%) of (±)-4, mp 192–194 °C. The racemate and enantiomers possessed identical spectral features. Anal. ($C_{16}H_{24}ClNO_2$) C, H, N.

X-Ray Crystallographic Studies. A crystal of (−)-**4a**·HCl crystallized from acetone was examined on a Syntex $P2_1$ diffractometer. The following cell data were obtained: a = 7.388(1) Å, b = 12.276(2) Å, c = 14.545(2) Å. The space group is $P2_12_12_1$, Z = 4, d_{calcd} = 1.22 g cm^{-3}. A total of 1240 reflections were obtained

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with monochromatic Cu Kα radiation using about 24 h for data collection in the ω scan mode.

The structure was found by classical Patterson and Fourier refinement methods, followed by full-matrix least-squares refinement computed on a Burroughs B6700. When the conventional R factor was 8.5%, examination of a difference map showed that the largest errors in the model were due to anisotropic vibration of the chloride ion and to the hydrogen atoms whose positions were obvious in this map. Full-matrix refinement with anisotropic temperature factor for the chloride ion only, keeping the H atoms B's constant, converged with an R factor of 4.8%. This refinement also included anomalous dispersion corrections to the atomic scattering factors for all non-H atoms. To determine the absolute configuration, the positions were changed to $\bar{x}$, $\bar{y}$, and $\bar{z}$ and refined in the same way as before. This refinement on the mirror form dropped the R factor to 3.1%, showing clearly that this second trial structure has the correct absolute configuration. Intense low-angle reflections were clearly affected by secondary extinction so that in these final refinements the 29 reflections having sine θ/λ less than 0.15 Å^{-1} were left out. The resulting structure is pictured in Figure 2 and the atomic positions are listed in Table II. The bond angles and distances along with standard deviations are given in Tables II and IV (see paragraph at the end of paper concerning supplementary material).

Opiate Receptor Binding. Guinea pig brain minus cerebellum homogenate was prepared as previously described.[17,18] The homogenate was prepared for the binding assay as 2% wet homogenate pellet weight in 100 mM Tris-HCl buffer without Na^+ present. [^{3}H]Etorphine (33 Ci/mmol, Amersham) was employed as the ^{3}H-labeled opiate ligand. The homogenate (250 μL), [^{3}H]etorphine (final concentration 2.5×10^{-9} M), varying concentrations of (+)-, (−)-, or (±)-**1b**, and Tris-HCl (to a final volume of 500 μL) were used in each determination. The homogenate was allowed 15 min equilibration time with the test compounds at 23 °C before the addition of the ^{3}H-labeled ligand and then incubated at 37 °C for 30 min prior to filtration (Whatman GF/B filters). The filters were placed in counting vials, and the [^{3}H]etorphine was solubilized from the membrane fragments by vortexing in 1 mL of absolute EtOH and counted in 10 mL of dioxane-based (Bray's solution) scintillation cocktail. Each concentration was run in quadruplicate samples, and the mean of the nondisplaced minus the mean of the displaced with 200X excess of levorphanol was plotted as probit values vs. log concentration. The IC_{50} values thus represent the ability of (−)-, (+)- and (±)-**4b** to displace 50% of the [^{3}H]etorphine bound at 2.5 nM concentration.

Acknowledgment. The authors are indebted to S. K. Guthrie for technical assistance, E. L. May of NIH, NIAMDD, for determination of analgetic activities, and to B. M. Cos of the Addiction Research Foundation, Palo Alto, CA, for help in setting up the opiate receptor binding assay. The research was supported in part by NIH Grant NS 05192 and a Scholarly Activity Grant made by the University of the Pacific to D.S.F.

Supplementary Material Available: Tables II–IV containing bond angles and distances along with standard deviations (2 pages). Ordering information is given on any current masthead page.

Isoxicam and Related 4-Hydroxy-*N*-isoxazolyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxides. Potent Nonsteroidal Antiinflammatory Agents

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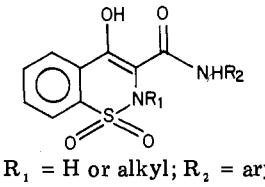
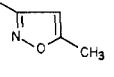
A novel series of antiinflammatory agents, *N*-isoxazolyl-3-carboxamides of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide, was synthesized and evaluated as antiinflammatory agents in the carrageenin-induced rat paw edema (CIRPE) assay and adjuvant-induced polyarthritis (AIP) assay. Several analogues were found to be equipotent or more potent than aspirin and phenylbutazone. Structure–activity relationships are discussed. One of the compounds, 4-hydroxy-2-methyl-*N*-(5-methyl-3-isoxazolyl)-2*H*-1,2-benzothiazine 3-carboxamide 1,1-dioxide (**3a**; isoxicam), was found to be 3 times as potent as phenylbutazone in the CIRPE and in the therapeutic AIP assays. Isoxicam (**3a**) is presently undergoing phase III clinical trial as an antiarthritic drug.

Independent studies in our laboratories,[1] as well as studies by Lombardino et al.,[2] have shown that certain enolizable amides (**1**) have useful antiinflammatory properties. More recently, Lombardino et al.[3] have reported that replacement of the aryl group (R_2) on the amide with

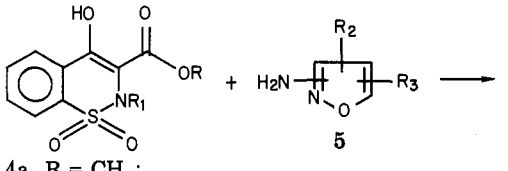


1, R_1 = H or alkyl; R_2 = aryl

2, R_1 = CH_3; R_2 =  or 

3a, R_1 = CH_3; R_2 = 

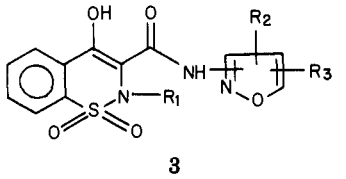
Scheme I



4a, R = CH_3; R_1 = H or CH_3

b, R = Et; R_1 = H or CH_3

5



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