(s, 2 H), 7.05–8.20 (m, 10 H). Anal. ($C_{25}H_{24}N_2O_5$) H, N; C: calcd, 69.43; found, 68.85.

Removal of *N*-*tert*-Butoxycarbonyl Group (12a–c). The *N*-(*tert*-butoxycarbonyl) derivatives (11a–c, 10–20 mg) were dissolved in trifluoroacetic acid (1 mL). After the mixture was allowed to stand for 30 min at room temperature, the trifluoroacetic acid was removed by passing a stream of N_2 over the solution. The residue was triturated with ether and the ether was discarded. The solid was dissolved in 1 mM aqueous HCl for use in the enzyme inhibition studies: NMR (D_2O) for **12a**: δ 4.40 (s, 2 H), 7.35 (s, 1 H), 7.45 (d, 1 H), 8.20 (d, 1 H). NMR (CD_3CN/D_2O) for **12b**: δ 4.35 (s, 2 H), 5.30 (s, 2 H), 7.15 (s, 1 H), 7.30 (d, 1 H), 7.40 (s, 5 H), 8.30 (d, 2 H); NMR (CD_3CN/D_2O) for **12c**: δ 4.40 (s, 2 H), 5.25 (s, 2 H), 7.10–8.25 (m, 10 H).

The compounds gave a single spot on TLC and were detected by UV absorption and ninhydrin. The solvents used were as follows: (A) 1-butanol–CH_3COOH–H_2O, 4:1:5; (B) EtOH–H_2O, 7:3. **12a**: R_f 0.54 solvent A, R_f 0.64 solvent B. **12b**: R_f 0.38 solvent A, R_f 0.75 solvent B. **12c**: R_f 0.59 solvent A, R_f 0.83 solvent B.

Acknowledgment. We are grateful to Dr. Bruce Furie for assistance in measuring partial thromboplastin times. We also thank Louise Robichaud for help in preparing this manuscript.

Registry No. **4**, 89-60-1; **5**, 26830-95-5; **6**, 90771-66-7; **7**, 100466-27-1; **8**, 100466-28-2; **9**, 100466-29-3; **10**, 100466-30-6; **11a**, 100466-31-7; **11b**, 100466-32-8; **11c**, 100466-33-9; **12a**, 100466-34-0; **12b**, 100466-35-1; **12c**, 100466-36-2; 4-(bromomethyl)-2-nitrobenzonitrile, 100466-37-3; di-*tert*-butyl dicarbonate, 24424-99-5; benzyl bromide, 100-39-0; 1-naphthylmethyl bromide, 3163-27-7; isotoic anhydride, 118-48-9; serine protease, 37259-58-8; chymotrypsin, 9004-07-3; trypsin, 9002-07-7; thrombin, 9002-04-4; plasmin, 9001-90-5.

Absolute Configuration of (–)-5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acid, the Active Enantiomer of Ketorolac[1]

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The (–)-*S* isomer of 5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid (1) is about 60 times more potent than the (+)-*R* isomer in the carrageenan edema test and ca. 230 times more active than the (+)-*R* isomer in the mouse phenylquinone writhing assay.

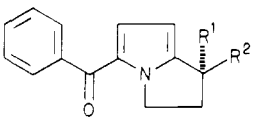
Ketorolac (1), a new α-substituted arylacetic acid with potent cyclooxygenase inhibitory activity, is a powerful antiinflammatory and analgesic agent in animal models.[3] In humans, it is essentially equivalent to morphine sulfate, on a weight basis, for the relief of moderate to severe postoperative pain.[4] This paper describes the resolution of ketorolac and the determination of the absolute configuration of the enantiomers.

Chemistry. The resolution of ketorolac was effected as follows. Crystallization of the cinchonidine salt from ethyl acetate gave the easily purifiable, less soluble salt of the (–) enantiomer. The more soluble salt was not readily obtained in optically pure form by recrystallization. Therefore, the crude, material from evaporation of the mother liquor was decomposed and the partially resolved (+) acid was converted into the cinchonine salt, which was diastereoisomerically pure after two crystallizations from ethyl acetate. Decomposition of the above salts with dilute sulfuric acid gave pure (–)- and (+)-ketorolac.[5]

The absolute configuration of the enantiomers was determined by a single-crystal X-ray analysis of the amide **2b** of (+)-(R)-1-(1-naphthyl)ethylamine and (+)-ketorolac. Inasmuch as the absolute configuration of the chiral center in the amine is known, that at C(1) in (+)-ketorolac was deduced to be *R* by internal reference.[6] Thus (–)-ketorolac must have the *S* absolute stereochemistry.

Results and Discussion

The antiinflammatory and analgesic activities of (+), (–), and racemic ketorolac were determined by using the carrageenan rat paw edema and mouse phenylquinone writhing assays, respectively. This side-by-side comparison shows (Table I) that essentially all of the pharmacological



(+)-(*R*)-**1**, R^1 = COOH; R^2 = H
(–)-(*S*)-**1**, R^1 = H; R^2 = COOH

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[∥] Syntex Research, Institute of Organic Chemistry.

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(2) Syntex Research Postdoctoral Fellow, 1983–1984.
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(5) Esterification of ketorolac with (–)-α-phenethyl alcohol (trifluoroacetic anhydride/triethylamine, benzene, 0–5 °C) gave a mixture of diastereoisomeric esters that was separable by HPLC [9 mm × 50 cm Lichrosorb SI 60 (10 μm), using hexane–ethyl acetate (96:4) at 1000 psig]. Cleavage of each diastereoisomerically pure ester, with 45% trifluoroacetic acid in benzene at room temperature (1.5–2 h), gave (+)- and (–)-ketorolac, both of which possessed rotations ca. 20° lower than the enantiomerically pure acids obtained by the classical procedure. It is evident that partial racemization had occurred during transesterification.
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0022-2623/86/1829-0589$01.50/0

Table I. Antiinflammatory and Analgesic Activities of (+)-(R)-, (−)-(S)-, and (RS)-Ketorolac (1)

compd	rat paw assay: phenylbutazone = 1[a]	mouse writhing assay: aspirin = 1[b]
(RS)-1	96 (48–252)[c]	399 (351–454)[c]
(+)-(R)-1	3 (2–7)	<3
(−)-(S)-1	170 (76–477)	699 (390–1311)

[a] ED_{50} = 15 mg/kg. [b] ED_{50} = 70 mg/kg. [c] 95% confidence limits.

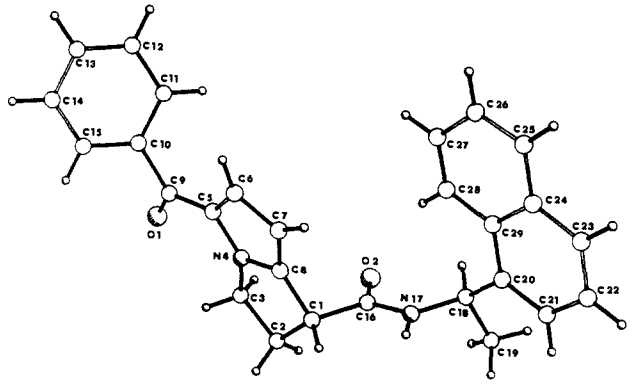

Figure 1. Computer-generated perspective drawing of R,R amide **2b**.

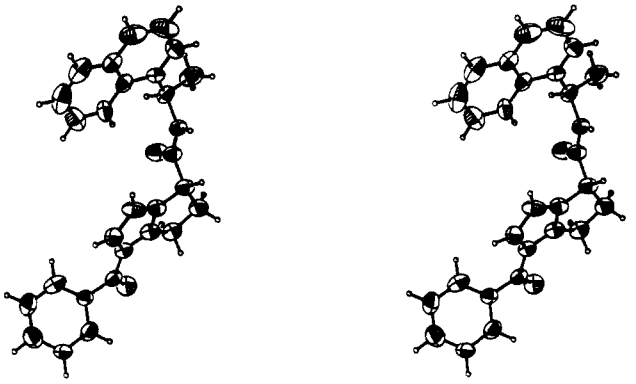

Figure 2. Stereoview of the R,R amide **2b** with thermal ellipsoids at the 50% probability level.

activity resides in the (−)-S isomer, which is ca. twice as potent as the racemate[7] in both assays. The active enantiomer of ketorolac thus has the same absolute stereochemistry as other α-substituted arylacetic acid antiinflammatory/analgesic agents such as naproxen[8] and clindanac.[9]

Figure 1 shows a computer-generated perspective drawing and Figure 2 a stereoview of the molecular configuration of the amide **2b**. There are two noteworthy features of the conformation of this molecule. Firstly, the bicyclic 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole system is very nearly flat with only C(2) being slightly out of the plane. Secondly, the ketone carbonyl group O(1)–C(9) and the pyrrole nucleus are essentially coplanar [signed torsion angle O(1)–C(9)–C(5)–N(4) = −3.5 (1)°] and the phenyl group is twisted out of this plane by nearly 60° torsion angle C(15–C(10)–C(9)–O(1) = +55.8 (1)°]. This situation is dramatically highlighted by the very different C(9)–C(10) and C(5)–C(9) bond distances of 1.516 and 1.418 Å, respectively (Table II, supplementary material): The former value is close to that expected (1.505 Å)[10] for a normal Ar–R carbon–carbon bond whereas the latter is indicative of substantial overlap of the pyrrole and carbonyl group π-systems. This orientation of the benzoyl group in ketorolac differs significantly from that observed for the *p*-chlorobenzoyl moiety of indomethacin.[11]

Experimental Section

The inhibition of the carrageenan-induced rat paw edema and the phenylquinone-induced mouse writhing assays were carried out as described in recent publications from these laboratories (ref 3 and references therein).

The melting points were determined in a Mel-Temp apparatus and are not corrected. The IR spectra were measured on a Perkin-Elmer Model 237 grating infrared spectrophotometer. The UV spectra were recorded in methanol solution with a Perkin-Elmer Model 402 ultraviolet–visible spectrometer. The optical rotations were determined with a Perkin-Elmer Model 141 recording polarimeter. The NMR spectra were recorded in $CDCl_3$ solution with a Varian EM-390 spectrometer and are expressed in parts per million (δ) from internal tetramethylsilane.

Crystals of the amide **2b** (see below) suitable for X-ray analysis were obtained from ethyl acetate. A needle-shaped crystal, with approximate dimensions 0.1 × 0.1 × 0.46 mm, was mounted on a Nicolet R3m automatic four circle diffractometer.

Crystal data: $C_{27}H_{24}N_2O_2$, M_r 408.48, monoclinic; a = 8.126 ± 0.003 Å, b = 15.824 ± 0.006 Å, c = 8.975 ± 0.003 Å, β = 112.01 ± 0.03°, V = 1069.94 Å^3, D_{calcd} = 1.27 g cm^{-3}, Z = 2, $F(000)$ = 432; space group $P2_1$, from systematic absences $0k0$ for k odd, μ(Mo Kα) = 0.75 cm^{-1}.

Crystallographic Measurements. The lattice constants were obtained from least-squares refinement of 15 reflections (5° < 2θ < 13°). Three-dimensional intensity data were measured by using graphite-monochromatized to Mo Kα radiation (λ = 0.71069 Å) by the ω-scan mode at variable scan rate (minimum 3.91°/min, maximum 29.3°/min) for 3° < 2θ < 45°. A total of 1462 independent reflections were collected, and intensities were corrected for the Lp factor but no absorption correction was made.

Structure Solution and Refinement. The crystal structure of **2b** was solved by direct methods and refined by a block-cascade least-squares procedure with anisotropic temperature factors for all non-hydrogen atoms and fixed isotropic temperature factor of U = 0.06 Å^2 for hydrogen. The hydrogen atom contributions have not been included and only the coordinates of the H atom bonded to N(17) were refined to a final weighted R = 0.0527 (unweighted R = 0.0553), using a weighted scheme $\omega^{-1}|\sigma^2(F_o) + G(F_o)^2|$ with G = 0.00101. This minimizes the function $\Sigma\omega|\Delta F|^2$ for 1069 reflections with $I > 1.7\sigma(I)$, no peaks > 0.2 e Å^3. The atomic scattering factors were taken from ref 12.

Computations were carried out using the SHELXTL system[13] on a NOVA 4/S computer.

The bond lengths and bond angles (Table II), the final atomic coordinates and U_{eq} values (Table III), hydrogen coordinates (Table IV), and anisotropic temperature factors (Table V) are available as supplementary material.

Resoltuion of 5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]-pyrrole-1-carboxylic Acid (1, Ketorolac). A solution of *l*-cinchonidine (11.77 g, 40 mmol) in hot ethanol (200 mL) was added to a solution of (±)-1 (10.20 g, 40 mmol) in ethyl acetate (50 mL). The resulting solution was heated at reflux temperature for 0.5 h, the solvent was removed in vacuo, and the residue was crystallized from ethyl acetate (200 mL). The salt that crystallized (4.7 g, 43%) had the following: mp 199–200 °C dec; $[\alpha]_D$ −217° (*c* 1, MeOH); UV 226, 245 (sh), 314 nm (ε 40700, 8910, 21400). Anal. ($C_{34}H_{35}N_3O_4$) C, H, N.[14]

(7) The pharmacological activities of (±)-ketorolac given in Table I are somewhat higher than those previously reported.[3]

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(12) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, 1974; Vol. 4.
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The mother liquor from the above crystallization was evaporated in vacuo, the residue was take up in ethyl acetate (200 mL), and the solution was shaken with 2 N sulfuric acid (75 mL). The organic phase was combined with an ethyl acetate extract of the aqueous phase, and the solution was washed with water and dried (magnesium sulfate). The solvent was removed in vacuo and the partially resolved acid (8 g, 31.4 mmol) was dissolved in ethanol (50 mL) and added to a suspension of cinchonine (9.24 g, 31.4 mmol) in hot ethanol (200 mL). The resulting solution was heated at reflux temperature for 0.5 h, the solvent was removed in vacuo, and the residual oil was dissolved in ethyl acetate (150 mL). After 2 h, the salt that crystallized [3.4 g; mp 174–175 °C; $[\alpha]_D$ +267° (*c* 1, MeOH)] was collected by filtration and recrystallized from ethyl acetate (75 mL). The pure cinchonine salt (2.13 g, 25%) had the following: mp 178–180 °C; $[\alpha]_D$ +271° (*c* 1, MeOH); UV 227, 245 (sh), 313 nm (ϵ 40 700, 8910, 21 400). Anal. ($C_{34}H_{35}N_3O_4$) C, H, N.

Dilute sulfuric acid (25 mL, 2 N) was added to a suspension of the above cinchonidine salt (4.7 g) in water (50 mL). The solution was extracted with ethyl acetate, and the extract was washed with water, dried, and evaporated in vacuo. The solid residue was recrystallized from hexane–ethyl acetate to give pure (−)-ketorolac (1.74 g, 80%): mp 169–170 °C; $[\alpha]_D$ −176° (*c* 1, MeOH). Anal. ($C_{15}H_{13}NO_3$) C, H, N.

Decomposition of the cinchonine salt in the manner described above gave the crude (+)-acid, which on crystallization from hexane–ethyl acetate gave pure (+)-ketorolac (75% yield): mp 174 °C; $[\alpha]_D$ +173° (*c* 1, MeOH). Anal. ($C_{15}H_{13}NO_3$) C, H, N.

To determine the effectiveness of the resolution of ketorolac, each antipode was esterified with excess ethereal diazomethane, and the esters were subjected to analysis by NMR spectroscopy in the presence of the chiral shift reagent $Pr(hfc)_3$. The racemic ester (0.030 g/0.6 mL of $CDCl_3$) showed two singlets for the enantiotopic methyl groups at δ 2.76 and 2.90 in the presence of the shift reagent (0.062 g). The (−)-methyl ester showed only one singlet at δ 2.90, indicating 100% enantiomeric purity. The enantiomeric purity of the (+) isomer can thus be calculated to be >98% on the basis of its optical rotation.

Synthesis of the Amides 2a and 2b of (+)-(*R*)-1-(1-Naphthyl)ethylamine and (−)- and (+)-5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids, Respectively. To a stirred suspension (0.51 g, 2 mmol) of (±)-1 and dicyclohexylcarbodiimide (0.452 g, 2.2 mmol) in dry dichloromethane (20 mL) was added the amine (0.32 mL; Aldrich Gold label, distilled).[15] After 4 h, this mixture was diluted with additional dichloromethane (30 mL) and filtered. The filtrate was washed successively with 1 N hydrochloric acid, 5% sodium bicarbonate solution, and water. Evaporation of the dried organic phase gave an oil, which solidified on standing. The diastereoisomeric mixture was separated by flash chromatography on silica gel (100 g) with hexane–ethyl acetate (3:2) as the eluting solvent. The less polar and more polar amides **2a** (0.282 g, 35%) and **2b** (0.251 g, 31%) were obtained as solids. In separate experiments, the amide **2a** (R_f 0.5, silica gel, 1:1 hexane–ethyl acetate) was obtained from (−)-1 and **2b** (R_f 0.3) was prepared from (+)-1.

On crystallization from ethyl acetate, **2a** had the following: mp 212–213 °C; $[\alpha]_D$ −164° (*c* 0.5, $CHCl_3$); UV 225, 248, 271, 281, 293, 311 nm (ϵ 74 100, 8320, 8710, 11 200, 14 100, 19 100); IR (KBr) 3285, 1640, 1630 cm^{-1}; NMR δ 1.60 (d, 3 H, *J* = 7 Hz), 2.78 (q, 2 H, *J* = 7.5 Hz), 3.80 (t, 1 H, *J* = 7.5 Hz), 4.20–4.70 (m, 2 H), 5.70–6.10 (m, 2 H), 6.10–6.40 (1 H, exchanged with D_2O), 6.76 (d, 1 H, *J* = 4.5 Hz), 7.30–7.70 (m, 7 H), 7.70–8.20 (m, 5 H). Anal. ($C_{27}H_{24}N_2O_2$) C, H, N.

Crystallization of **2b** from hexane–ethyl acetate gave a solid: mp 222–223 °C; $[\alpha]_D$ +126° (*c* 0.5, $CHCl_3$); UV 224, 248, 271, 281, 293, 312 nm (ϵ 69 200, 8320, 8510, 11 200, 13 500, 18 200); IR (KBr) 3325, 1670, 1595 cm^{-1}; NMR δ 1.70 (d, 3 H, *J* = 7 Hz), 2.80 (q, 2 H, *J* = 7.5 Hz), 3.86 (t, 1 H, *J* = 7.5 Hz), 4.15–4.65 (m, 2 H), 5.73–6.07 (m, 2 H), 6.10–6.35 (1 H, exchanged with D_2O), 6.75 (d, 1 H, *J* = 4.5 Hz), 7.30–7.70 (m, 7 H), 7.70–8.20 (m, 5 H). Anal. ($C_{27}H_{24}N_2O_2$) C, H, N.

Acknowledgment. One of us (R.A.T) thanks Dr. M. Soriana-Garcia for helpful discussions and for his assistance in the crystal structure determination and A. Cuellar for technical assistance.

Supplementary Material Available: Bond lengths and bond angles (Table II), final atomic coordinates and U_{eq} values (Table III), hydrogen coordinates (Table IV), and anisotropic temperature factors (Table V) (8 pages). Ordering information is given on any current masthead page.

(14) The elemental analysis of the new compounds described in the Experimental Section were within ±0.4% of the calculated values.

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Book Reviews

The Chemistry and Biology of Isoquinoline Alkaloids. Edited by J. D. Phillipson, M. F. Roberts, and M. H. Zenk. Springer-Verlag, Berlin-Heidelberg-New York-Tokyo. 1985. vii + 304 pp. 17 × 23 cm. ISBN 3-540-13980-X. $39.00.

The Chemistry and Biology of Isoquinoline Alkaloids is the proceedings volume edited on the basis of the plenary lectures presented at a 3-day symposium arranged by the Phytochemical Society of Europe in London in April 1984. The chapters cover the recent progress of research on the isolation, structure elucidation, synthesis, pharmacology, structure–activity investigation, and biosynthesis and catabolism, as well as production by plant cell culture techniques, of the isoquinoline alkaloids. The titles of lectures and the authors are as follows:

"Plants as a Source of Isoquinoline Alkaloids" (N. G. Bisset), "Chemotaxonomy of the Papaveraceae Alkaloids" (V. Preininger), "Structure Activities and Pharmacological Properties of the Opium Alkaloids" (E. Lindner), "The Occurrence of Simple Isoquinolines in Plants" (J. Lundstrom), "*Erythrina* Alkaloids" (A. H. Jackson), "Annonaceae Alkaloids" (A. Cave), "The Chemistry and Pharmacology of Cularine Alkaloids" (L. Castedo), "Bisbenzylisoquinoline Alkaloids" (P. L. Schiff, Jr.), "Natural Degradative Routes for the Aporphines" (M. Shamma), "Synthesis and Structure–Activity Relationships of Aprophines as Dopamine Receptor Agonists and Antagonists" (J. L. Neumeyer), "The Chemistry and Pharmacology of Morphinan Alkaloids" (A. Brossi), "The Development of a Practical Total Synthesis of Natural and Unnatural Codeine, Morphine and Thebaine" (K. C. Rice), "Biomimetic and Total Synthesis of Monoterpenoid Isoquinoline Alkaloids" (R. B. Herbert), "Biosynthesis of Morphinan Alkaloids" (E. Brochmann-Hanssen), "Enzymology of Benzylisoquinoline Alkaloid Formation" (M. H. Zenk), "Morphinan Alkaloids from Plant Cell Cultures" (F. Constabel), "The Production of Isoquinoline Alkaloid Accumulation" (T. M. Kutchan, S. Ayabe, C. J. Coscia).

The volume also includes a brief subject index.

All the authors describe their topic where they have made considerable contribution in detail and standards. In addition to the referecnes, the majority of the chapters contain suggested reading for the topic reviewed that helps the readers in broadening their knowledge on the particular group of alkaloids.

In summary, *The Chemistry and Biology of Isoquinoline Alkaloids* presents an interesting and current discussion of a