pretreatment cultures of cells were grown in 25-cm^2 disposable plastic tissue culture flasks, and before drug and X-ray treatment, the flasks received fresh complete medium and were ventilated with humidified gas consisting of 95% N_2 and 5% CO_2 for 4 h at 37 °C with very gentle agitation. Drug was then added via a syringe so as to introduce no O_2. Irradiation procedures and the subsequent colony-forming assay were as described above for oxic conditions.

Acknowledgment. We express our thanks to Dr. William C. Rose of Bristol-Myers Co. for the antitumor screening data. This work was supported by a research grant from the National Cancer Institute (RO1-CA06695-24).

Registry No. 4, 113811-39-5; 5, 113811-41-9; chloranil, 118-75-2; 2-aminoethanol, 141-43-5; 2,5-bis[(2-hydroxyethyl)amino]-3,6-dichloro-1,4-benzoquinone, 28857-12-7; 2,5-bis[[(dichlorophosphinyl)[(carbamoyloxy)ethyl]amino]-3,6-dichloro-1,4-benzoquinone, 113811-38-4; 2,2-dimethylazinidine, 2658-24-4; 2-(hydroxymethyl)anthraquinone, 17241-59-7; 2-[(dichlorophosphinyl)carbamoyloxymethyl]anthraquinone, 113811-40-8.

Synthesis and Analgesic Activity of Pemedolac (*cis*-1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic Acid)†

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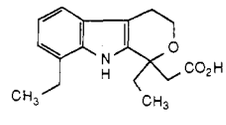
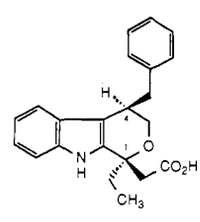
The synthesis of *cis*-1-ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic acid, pemedolac (USAN), is described. This compound has been found to be a potent analgesic agent in primary screening. Pemedolac has been resolved and the active (+)-enantiomer assigned a 1*S*,4*R* absolute configuration on the basis of a crystallographic analysis of its (*S*)-(−)-borneol ester.

In 1976 we disclosed the discovery of a novel antiinflammatory agent, 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetic acid, etodolac.[1] Since then, etodolac has progressed successfully through clinical studies and has been demonstrated to be an effective agent possessing an exceptional gastrointestinal safety profile in humans.[2] Like many other nonsteroidal antiinflammatory drugs, etodolac also possesses analgesic properties.[3] Continued investigations of the pyrano[3,4-*b*]indole-1-acetic acids have now led to a new series of agents exhibiting a marked separation of the levels of these activities. One member, *cis*-1-ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano-[3,4-*b*]indole-1-acetic acid, pemedolac (**13**), a highly potent analgesic with relatively weak antiinflammatory properties, has been chosen for further study and is currently being evaluated in humans. We report the synthesis, primary pharmacology, and X-ray structural determination of pemedolac (**13**) and its enantiomers.



etodolac

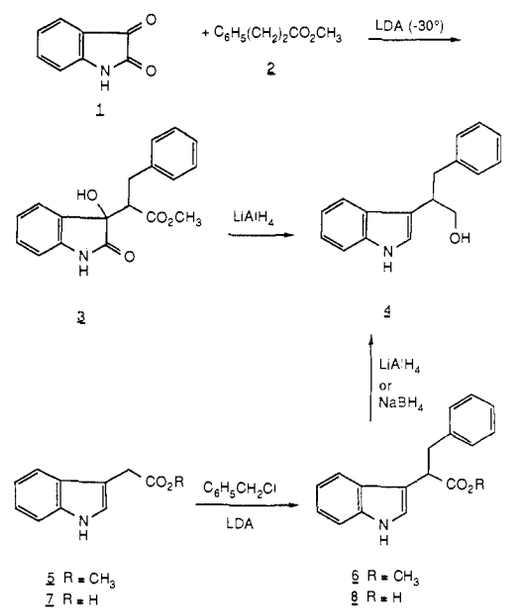


pemedolac 13

Chemistry

Synthesis of pemedolac (**13**) was achieved as shown in Scheme I. The enolate of methyl phenylpropionate (**2**) was trapped by isatin (**1**) to form adduct **3**. Quantitative conversion was not observed; even when large excess of the enolate of **2** was utilized, unreacted isatin remained after workup. The crude adduct **3**, a mixture of diastereomers,

Scheme I



1 2 3 4

5 R = CH_3 6 R = CH_3
7 R = H 8 R = H

was treated with excess $LiAlH_4$ in tetrahydrofuran to afford β-(phenylmethyl)indole-3-ethanol (**4**) in a 72% yield. Indole, resulting from reduction of unreacted isatin, was obtained as a byproduct.

An alternate approach to β-(phenylmethyl)indole-3-ethanol (**4**) has been devised. The dianion of methyl indole-3-acetate (**5**), formed by treatment with lithium diisopropylamide (LDA) in tetrahydrofuran at −30 °C, was alkylated with benzyl chloride to afford adduct **6**. Upon reduction with sodium borohydride in methanol, β-(phenylmethyl)indole-3-ethanol (**4**) was obtained together with tryptophol. The latter presumably could have come from

† This paper is dedicated to Prof. E. C. Taylor by one of us (A.H.K.) on the occasion of his 65th birthday.
‡ Princeton, New Jersey.
§ Montreal, Canada.
⊥ Princeton University.

(1) Demerson, C. A.; Humber, L. G.; Philipp, A. H.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 391.
(2) Humber, L. *Med. Res. Rev.* **1987**, *7*, 1.
(3) Martel, R. R.; Klicius, J. *Can. J. Physiol.* **1976**, *54*, 245.

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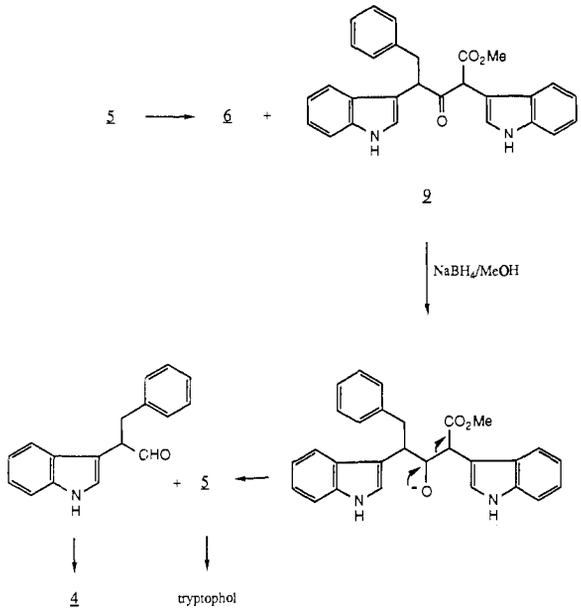
Scheme II



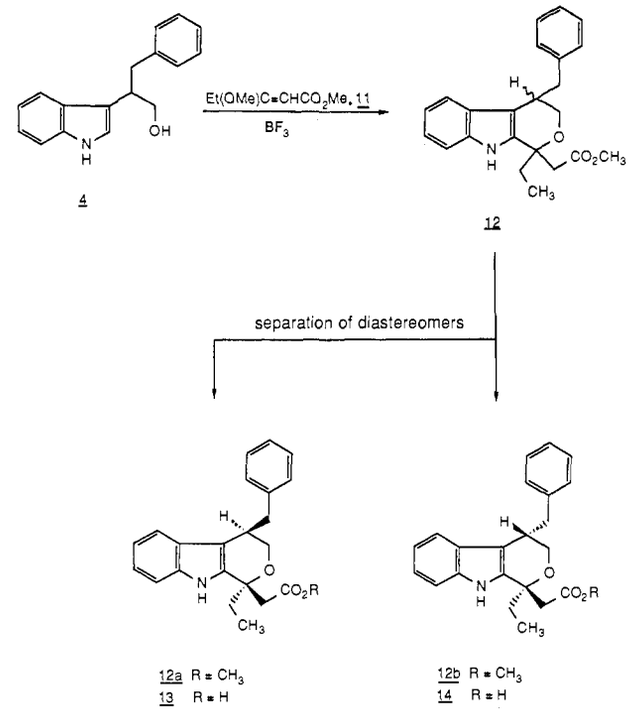
reduction of unreacted **5**; however, reexamination of the crude adduct **6** by HPLC found it to be free of methyl indole-3-acetate but contaminated with an unidentified polar product. We speculate that this may be dimeric product **9**, which undergoes reduction as in Scheme II to produce tryptophol.

The formation of tryptophol could be avoided if the alkylation with benzyl chloride was carried out on the trianion of indole-3-acetic acid (**7**), generated with an excess of LDA at −5 to −10 °C. Under these conditions acid **8** was produced in a 96% yield. Subsequent esterification and reduction gave β-(phenylmethyl)indole-3-ethanol (**4**) free of tryptophol.

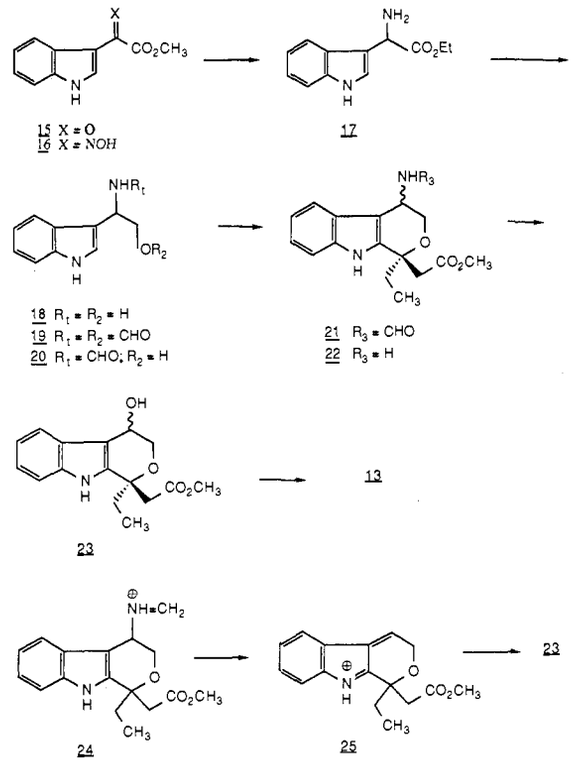
Pyrano[3,4-*b*]indole ring formation was achieved by a variation of the method previously reported.[1,4] Condensation of **4** with methyl propionylacetate or the corresponding enol ether **11** in dichloromethane in the presence of boron trifluoride etherate gave a 1:1 mixture of the diastereomeric esters **12** (Scheme III). When the reaction was done in toluene at −15 °C, a 2:1 ratio favoring the less polar ester **12a** was obtained. The diastereomers **12** could be separated by flash chromatography or by fractional crystallization. Hydrolysis of each ester, **12a** and **12b**, provided the corresponding acids, pemedolac (**13**) and the diastereomer **14**.

A stereoselective synthesis has been developed in which the benzyl group is introduced with the correct configuration to the preformed pyrano[3,4-*b*]indole system, as shown in Scheme IV. The key intermediate, the formamido derivative **20**, was prepared from methyl indole-3-glyoxylate (**15**). Conversion to oxime **16** and successive reductions gave amino ester **17** and β-aminoindole-3-ethanol (**18**). Attempts to generate the 4-amino methyl ester **22** directly from **18** were unsuccessful, as no cyclization occurred. The formamido compound **20**, obtained from the *O*,*N*-diformyl derivative **19** by selective hydrolysis, reacted with the methyl 3-methoxy-2-propionate in the presence of boron trifluoride etherate to give the 4-formamidopyrano[3,4-*b*]indole **21** as a 1:1 mixture of diastereomers. Hydrolysis of the formamido esters **21** afforded amino esters **22**, which, when treated with paraformaldehyde in aqueous tetrahydrofuran at reflux, yielded

Scheme III



Scheme IV



the 4-hydroxy esters **23**. While the precise mechanism of the formation of **23** from **22** is unknown, it can be postulated that the indolenine **25** is the intermediate that leads directly to the 4-hydroxy ester. The required presence of paraformaldehyde for the reaction to proceed suggests that it facilitates the elimination of the 4-substituent by the formation of a species such as **24**. Treatment of the hydroxy ester **23** with benzylmagnesium chloride at −78 °C in the presence of titanium tetrachloride afforded esters **12** in a ratio of 3:1. Subsequent hydrolysis and crystallization gave pemedolac (**13**) and its diastereomer **14** in a ratio of 10:1.

(4) Demerson, C. A.; Humber, L. G.; Dobson, T. A.; Martel, R. R. *J. Med. Chem.* **1975**, *18*, 189.

Table I. Analgesic, Antiinflammatory, and Ulcerogenic Properties of Pemedolac versus Reference Standards

experimental test[a]	pemedolac (13)	etodolac	piroxicam	ibuprofen
mouse PBQ writhing: ED_{50}, mg/kg po (95% CL)	2.0 (0.5–8.3)	168 (117–241)	3.4 (1.6–6.9)	32.4 (21.5–49)
rat Randall–Selitto: ED_{50}, mg/kg po (95% CL)	0.003[b] (<0.38)	4.5 (3.0–6.8)	0.35 (0.18–0.66)	64.5 (33–126)
rat carrageenan paw edema: ED_{50}, mg/kg po (95% CL)	~100[c]	23 (10–51)	1.3	21
antiinflammatory/analgesic ratio[d]	~33000	5.1	3.7	0.3
rat acute ulcerogenesis: UD_{50}, mg/kg po (95% CL)	107 (68–168)	58 (36–84)	6.0 (3.1–11.6)	150 (95–237)
analgesic safety index[e]	>35000	13	17	2.3

[a] The ED_{50} in the PBQ writhing test represents the dose at which 50% inhibition of writhing would occur. The ED_{50} in the Randall–Selitto test was the dose causing an analgesic effect in 50% of the rats. The ED_{50} in the carrageenan paw edema assay was the dose causing 50% inhibition of edema. The UD_{50} represents the dose at which 50% of the rats had a positive gastrointestinal irritation/ulceration on a quartal all-or-none basis. [b] The analgesic dose–response curve was relatively flat over the 0.001–0.1 mg/kg range. [c] Estimated ED_{50}: 48% inhibition at 100 mg/kg. [d] Ratio of carrageenan paw edema ED_{50}/Randall–Sellitto ED_{50}. [e] Ratio of acute ulcerogenesis UD_{50}/Randall–Selitto ED_{50}.

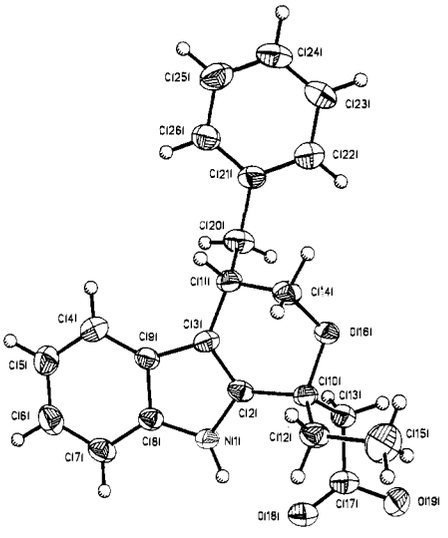


Figure 1. ORTEP-like drawing of (±)-pemedolac (**13**), computer generated by SHELXTL software.[9] C-1 and C-4 carbons are labeled C(10) and C(11), respectively.

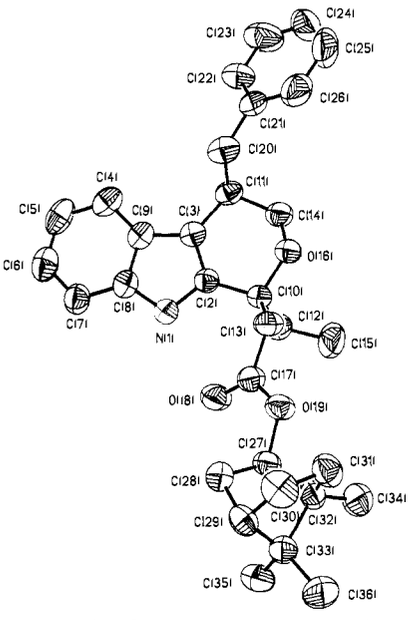


Figure 2. ORTEP-like drawing of the (*S*)-(−)-bornyl ester of (+)-pemedolac (**13a**), computer generated by SHELXTL software.[9]

An X-ray crystallographic analysis was done on pemedolac (**13**) in order to determine the relative configuration of the chiral centers at C-1 and C-4. Figure 1 is an ORTEP-like drawing of the final crystallographic model, which establishes that the benzyl group at C-4 and the acetic acid moiety at C-1 are cis.

Pemedolac (**13**) was resolved by conversion to its diastereomeric esters with (−)-borneol followed by preparative HPLC.[5] Upon hydrolysis each enantiomer, **13a** and **13b**, was obtained in high optical purity, as determined by esterification of the acids with diazomethane and performing HPLC analysis on a chiral column. The absolute stereochemistry of the (+)-enantiomer **13a** was ascertained by X-ray crystallography of its (*S*)-(−)-bornyl ester. The structure is shown in Figure 2. The X-ray crystallographic analysis has shown that this enantiomer has the same stereochemistry at C-1 as the active 1*S* enantiomer of etodolac.[6] Indeed, pemedolac differs only in lacking the 8-ethyl group and possessing a 4-benzyl group. The 1*S*,4*R* absolute stereochemistry is shown stereoscopically in Figure 3.

Biology: Results and Discussion

The analgesic properties of pemedolac (**13**) were first determined in the mouse phenylbenzoquinone (PBQ) writhing and rat Randall–Selitto assays (Table I).

In the mouse model, pemedolac had an ED_{50} of 2 mg/kg po, making it equipotent with piroxicam, 16-fold more potent than ibuprofen, and 84-fold more potent than etodolac. In the Randall–Selitto assay, pemedolac was the most potent agent tested, having an ED_{50} of 0.003 mg/kg po, some 100 times less than the ED_{50} of piroxicam.

Investigation of the antiinflammatory effect in an acute model of inflammation, the carrageenan paw edema assay, showed that pemedolac has a particularly wide spread between doses that exhibit antiinflammatory activity and those that produce an analgesic effect. Because pemedolac has a shallow dose–response curve in the Randall–Selitto assay, at a dose of 0.1 mg/kg po, 75% of the rats exhibited an analgesic effect, the ratio can be only estimated to be 33 000. This is well above the values of 5.1 for etodolac and 3.7 for piroxicam. The effects of pemedolac in other analgesic models will be reported elsewhere.

A common drawback of nonsteroidal antiinflammatory drugs is their ulcerogenic liability. To assess this property, Sprague–Dawley rats were fasted for 8 h and then administered pemedolac po. After 18 h the rats were euthanized, and their stomachs were examined for the presence of lesions. By this technique, pemedolac was found to have an acute UD_{50} of 107 mg/kg po. Thus, the safety index was over 35 000 if one compares the ratio of UD_{50} to ED_{50} in the Randall–Selitto paw pressure assay. This safety index is greater than that of any analgesic drug so far tested in our laboratories or reported in the literature. It should be noted that upon multiple dosing the UD_{50} for producing intestinal lesions was 140 mg/kg per day po. This data as part of the full pharmacological

(5) Demerson, C. A.; Humber, L. G.; Abraham, N. A.; Schilling, G.; Martel, R. R.; Pace-Asciak, C. *J. Med. Chem.* **1983**, *26*, 1778.
(6) Humber, L. G.; Demerson, C. A.; Swaminathan, P.; Bird, P. H. *J. Med. Chem.* **1986**, *29*, 871.

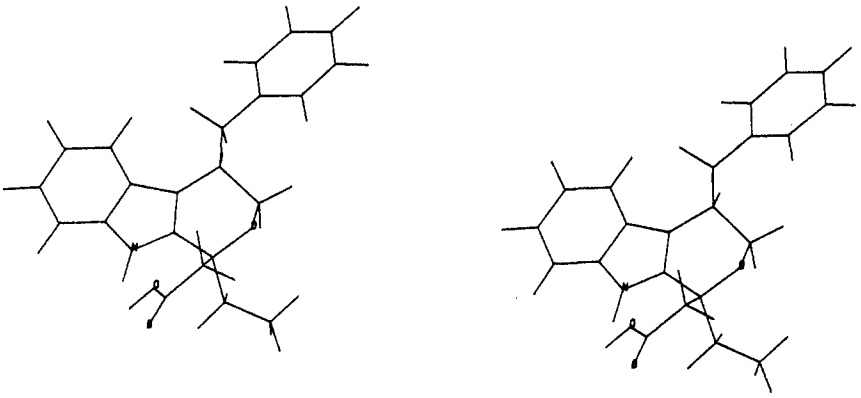


Figure 3. Stereoscopic view of (+)-pemedolac (**13a**).[15]

Table II. Analgesic Properties of Pemedolac Isomers

compound	mouse PBQ writhing: ED_{50}, mg/kg po	Randall–Selitto: ED_{50}, mg/kg po
(+)-pemedolac[a] (**13a**)	1.8 (0.6–5.2)	0.04 (0.012–0.13)
(−)-pemedolac (**13b**)	15% inhibition at 30 mg/kg	40% analgesic effect at 10 mg/kg
trans isomer 14	19% inhibition at 25 mg/kg	NT[b]

[a] 95% Confidence limits. [b] NT = not tested.

profile of pemedolac will be reported elsewhere.

The trans diastereomer of pemedolac, **14**, was not active at 25 mg/kg po in the PBQ writhing assay (Table II). The stereospecific action of pemedolac is further evident upon examination of its enantiomers. Most, if not all, of the analgesic effect resides in the (+)-enantiomer **13a**.

The reason for the higher analgesic potency of pemedolac relative to that of etodolac is not known. It may be that there is π-binding of the benzyl group with an accessory binding site on a receptor. Another possibility is that the benzyl group in causing increased lipophilicity[7] optimizes the pharmacokinetic requirements for the transportation of the molecule to an analgesic site of action.[8]

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography was performed with E. Merck Kieselgel $60F_{254}$ plates. E. Merck Kieselgel 60 (230–400 mesh) was used for flash chromatography. ^1H NMR spectra were recorded on a Varian XL-200 instrument. Microanalyses were done on a Control Equipment Corp. modified Perkin-Elmer 240 analyzer. Infrared spectra were recorded on a Perkin-Elmer 781 IR spectrophotometer. Analytical HPLC were conducted on a Waters μPorasil silica column with ethyl acetate–hexane mixtures as the mobile phase. The enantiomeric ratios were determined on a Regis L-phenylglycine Pirkle Covalent column with 2% 2-propanol–hexane as the mobile phase. A Waters Model 481 Lambda-Max variable wavelength absorbance detector was used. Preparative HPLC were performed on a Waters Prep 500A instrument equipped with two silica gel cartridges.

β-(Phenylmethyl)indole-3-ethanol (4). Method A. A stirred solution consisting of isatin (10.0 g, 0.068 mol), methyl 3-phenylpropionate (11.1 g, 0.068 mol), and THF (250 mL) was cooled to −5 °C. LDA (75 mL of a 1.92 M cyclohexane solution; Lithco) was added at such a rate as not to allow the internal temperature to rise above 0 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for 1 h, the cooling source was removed, and the mixture was allowed to reach room temperature and then heated to reflux for 20 min. After the mixture was cooled to room temperature, the excess LDA was quenched with saturated ammonium chloride solution. The phases were separated. The aqueous phase was extracted with ether (2 × 200 mL) and combined with the organic phase. $MgSO_4$ (100 g) and activated charcoal (5 g) were added and filtered through a pad of silica gel (200 g) and Celite (50 g). Concentration of the filtrate provided 21 g of **methyl 2,3-dihydro-3-hydroxy-2-oxo-α-(phenylmethyl)-1*H*-indole-3-acetate (3)**. Further purification was not necessary, although a TLC indicated the presence of a small amount of unreacted isatin. Crude **3** was dissolved in THF (100 mL), and the resulting solution was added to a stirring mixture of $LiAlH_4$ (7.5 g, 0.2 mol) in THF (300 mL). The reaction was refluxed for 1.5 h. The excess hydride was destroyed by the careful addition of THF–water (1:1) until foaming ceased. Aqueous HCl (50 mL, 1 N) was added, the reaction mixture was filtered, and the pad was washed with ether (400 mL). The filtrate was concentrated, and the residue was dissolved in EtOAc. TLC indicated the presence of indole. The solution was then washed with 1 N HCl (400 mL), 5% $NaHCO_3$ (2 × 200 mL), and water (200 mL). $MgSO_4$ and charcoal (5 g) were added, and the solution was filtered through a pad of silica gel (200 g) and Celite (50 g). Concentration gave 12.3 g (72% from isatin) of **4** as a viscous oil: NMR ($CDCl_3$) δ 8.08 (s, 1 H), 7.65 (d, 1 H, J = 7.5 Hz), 7.36 (d, 1 H, J = 7.5 Hz), 7.18 (m, 7 H), 7.01 (d, 1 H, J = 2.0 Hz), 3.84 (d, 2 H, J = 5.0 Hz), 3.43 (m, 1 H), 3.10 (d, 2 H, J = 8.0 Hz), 1.79 (s, 1 H). Anal. ($C_{17}H_{17}NO$) H, N; C: calcd, 81.24; found, 80.79.

Method B. To a 2-L three-necked round-bottom flask equipped with an addition funnel was added, under nitrogen, 300 mL of dry THF and 68.75 mL of LDA (1.92 M in cyclohexane–THF, 0.0132 mol). The solution was cooled to −78 °C, and a solution of methyl indole-3-acetate (11.36 g, 0.060 mol) in 300 mL of dry THF was added dropwise. After 15 min, a solution of benzyl chloride (7.59 g, 0.060 mol) in THF (300 mL) was added dropwise. The reaction mixture must be stirred vigorously so that the precipitated dianion of methyl indole 3-acetate reacts completely with the benzyl chloride. After 3 h, TLC analysis indicated complete consumption of starting material, and 200 mL of aqueous saturated ammonium chloride were added. The aqueous layer was separated and washed with ether (2 × 100 mL). The combined ether extracts were added to the organic layer, which was dried over $MgSO_4$, filtered, and concentrated to give 15.0 g (89% yield) of **methyl α-(phenylmethyl)indole-3-acetate (6)** as a red-brown oil. TLC of the crude oil showed it to be mainly **6**, contaminated with a polar product. On standing the oil slowly crystallized. Trituration with heptane afforded 11.6 g (69%) of **6** as fine white crystals, mp 62–68 °C: NMR ($CDCl_3$) δ 8.09 (s, 1 H), 7.73 (d, 1 H, J = 7 Hz), 7.40–7.09 (m, 9 H), 4.19 (dd, 1 H, J = 6.5 Hz, J = 2.2 Hz), 3.59 (s, 3 H), 3.47 (dd, 1 H, J = 13.5 Hz, J = 9.1 Hz), 3.20 (dd, 1 H, J = 13.5 Hz, J = 6.3 Hz). Anal. ($C_{18}H_{17}NO_2$) C, H, N.

A 250-mL, three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a condenser was charged with a

(7) The log P values for pemedolac and etodolac were 4.385 and 3.47, respectively. These were calculated with the CLOGP3 program in MEDCHEM, version 3.51, distributed by the Medicinal Chemistry Project, Pomona College, Claremont, CA.

(8) Mobilio, D.; Humber, L. G.; Katz, A. H.; Demerson, C. A.; Hughes, P.; Brigance, R.; Conway, K.; Shah, U.; Williams, G.; Labbadia, F.; DeLange, B.; Schmid, J.; Newburger, J.; Jensen, N. P.; Weichman, B. M.; Chau, T.; Neumann, G.; Wood, D. D.; Van Engen, D.; Taylor, N. *J. Med. Chem.*, in press.

solution of methyl α-(phenylmethyl)indole-3-acetate (6) (11.6 g, 0.0415 mol) in THF (60 mL). To this solution was added 3.65 g of sodium borohydride in one lot, while being stirred under nitrogen at 65–70 °C. To the above mixture was added dropwise methanol (18 mL) over a period of 8 h, and the resulting mixture was stirred at 60–70 °C overnight. TLC of a worked-up sample showed no starting material. The reaction mixture was cooled to 10 °C. In a portionwise manner cold water (60 mL) was added over a 15-min period, the mixture was stirred for 10 min, toluene (100 mL) was added, and the mixture was stirred vigorously for 15 min. The mixture was transferred to a separatory funnel, and the aqueous phase was separated and extracted with toluene (50 mL). The toluene extracts were combined and washed with water (80 mL × 2), 10% hydrochloric acid (50 mL), and again with water (80 mL × 4). The organic phase was filtered, and the filtrate was evaporated under reduced pressure to afford 9.62 g (92%) of 4. When the reduction was carried out as above with crude 6, an oil, a mixture of two products, was obtained. Flash chromatography on silica gel with 3:1 hexane–EtOAc afforded pure 4 and tryptophol (identified by NMR) in a 2:1 ratio.

Method C. A 1-L, three-necked flask equipped with a mechanical stirrer, a low-temperature thermometer, and a dropping funnel was flushed with nitrogen, charged with 400 mL of LDA in THF–cyclohexane solution (1.93 M; 0.772 mol), and cooled to −10 °C. This this cold solution was added a solution of indole-3-acetic acid (33.78 g, 0.193 mol) in THF (150 mL) over a period of 1 h, while the pot temperature was maintained at the range of −5 to −10 °C. Some precipitate formed during the addition. After being stirred at −5 °C for 2 h, the reaction mixture was cooled to −10 °C, and benzyl chloride (53.6 g, 0.424 mol) was added over a period of 30 min. The reaction temperature was allowed to warm to room temperature, and the mixture was stirred for 18 h. The reaction mixture was again cooled to −10 °C, and 150 mL of water was added. The mixture was evaporated under reduced pressure to remove about 70 mL of THF taken into toluene (200 mL) and water (100 mL), and the phases were separated. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give 49 g (96%) of solid **α-(phenylmethyl)indole-3-acetic acid (8)**. A sample was recrystallized from ether–hexane (mp 152–154 °C): NMR (DMSO-d_6) δ 3.06 (dd, 1 H, J = 13.5 Hz, J = 7.0 Hz), 3.35 (dd, 1 H, J = 13.5 Hz, J = 8.5 Hz), 4.06 (dd, 1 H, J = 8.1, J = 6.8 Hz), 6.96 (m, 1 H), 7.08 (m, 1 H), 7.14 (m, 1 H), 7.18–7.20 (m, 5 H), 7.33 (m, 1 H), 7.63 (m, 1 H), 10.93 (br s, 1 H, D_2O exchangeable), 12.15 (br s, 1 H, D_2O exchangeable); IR (KBr) 3390, 1700 cm^{-1}.

Methyl α-(phenylmethyl)indole-3-acetate, described above, was prepared by stirring a solution of α-(phenylmethyl)indole-3-acetic acid (12 g, 0.0453 mol) in MeOH (200 mL) containing 2 mL of concentrated sulfuric acid at reflux for 2 h. Usual workup afforded 6 (97%). See method B for the reduction to 4.

1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic Acid Methyl Ester (12) (Mixture of Isomers). A 250-mL, three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a low-temperature thermometer was charged with a solution of BF_3·Et_2O (10.9 g, 0.0767 mol) in dry toluene (45 mL). After the solution was cooled to 0 °C, methyl propionylacetate (5.0 g, 0.0383 mol) was added, and this solution was stirred under nitrogen at −15 °C. To this cold solution a solution of β-(phenylmethyl)indole-3-ethanol (4) (9.62 g, 0.379 mol) in dry toluene (30 mL) was added dropwise while the pot temperature was maintained at −15 to −10 °C. The reaction was stirred at −15 °C overnight. Pyridine (9 mL) was added over a period of 15 min while the temperature was maintained below 10 °C. Water (30 mL) was then added, and the phases were separated. The aqueous phase was extracted with toluene (3 × 40 mL). The combined organic layers were washed with water (2 × 50 mL), 10% HCl (40 mL), and again with water (3 × 50 mL). Evaporation under reduced pressure afforded 13.5 g (98%) of ester 12 as a 2:1 mixture of diastereomers (HPLC analysis) that solidified on standing.

***cis*-1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic Acid Methyl Ester (12a).** The diastereomeric mixture 12 is separable by silica gel flash chromatography. The first eluted compound (9:1 hexane–ethyl acetate) is 12a. Alternatively 12a can be isolated by a fractional crystallization from 2-propanol. In a typical run, 4.3 g of 12 was dissolved in hot 2-propanol. After 3 h a mass of fine crystals was filtered off. Repetition twice more afforded 1.6 g of 12a, mp 118.5–120 °C, with a diastereomeric purity of 98% as determined by HPLC analyses: NMR ($CDCl_3$) δ 9.17 (s, 1 H), 7.42–7.00 (m, 9 H), 3.80 (m, 2 H), 3.72 (s, 3 H), 3.20 (m, 2 H), 3.01 (d, 1 H, J = 17 Hz), 2.80 (d, 1 H, J = 17 Hz), 2.85 (m, 1 H), 2.05 (q, 2 H, J = 7.5 Hz), 0.90 (t, 3 H, J = 7.5 Hz); IR (KBr) 3420, 1725 cm^{-1}. Anal. ($C_{23}H_{25}NO_3$) C, H, N.

***trans*-1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic Acid Methyl Ester (12b).** The second minor compound eluted by flash chromatography of the diastereomeric mixture 12 with 9:1 hexane–EtOAc was 12b, a viscous oil: NMR ($CDCl_3$) δ 8.88 (s, 1 H), 7.38–7.00 (m, 9 H), 3.84 (m, 2 H), 3.70 (s, 3 H), 3.04 (d, 1 H, J = 17.5 Hz), 2.78 (d, 1 H, J = 17.5 Hz), 3.15 (m, 2 H), 2.82 (m, 1 H), 2.20 (q, 2 H, J = 7.5 Hz), 0.82 (t, 3 H, J = 7.5 Hz); IR (KBr) 3440, 1725 cm^{-1}.

***cis*-1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic Acid (Pemedolac, 13).** The methyl ester 12a (3.0 g, 0.0825 mol) was dissolved in EtOH (100 mL), and 10% aqueous NaOH (100 mL) was added. The mixture was heated under reflux for 2 h and then concentrated to a cloudy aqueous solution. Concentrated HCl was added until the mixture was acidic. It was then extracted with ether (2 × 100 mL), and the combined ether extracts were dried ($MgSO_4$), filtered, and concentrated to give 2.8 g of an off-white foam. This material was recrystallized from benzene–petroleum ether to give 2.30 g (80%), mp 145–147 °C: NMR ($CDCl_3$) δ 8.70 (s, 1 H), 7.43–7.03 (m, 9 H), 3.87 (d, 2 H, J = 2.5 Hz), 3.23 (m, 2 H), 2.97 (d, 2 H, J = 3.0 Hz), 2.85 (m, 1 H), 2.04 (m, 2 H), 0.93 (t, 3 H, J = 7.5 Hz); IR (KBr) 3380, 3260, 1740 cm^{-1}. Anal. ($C_{22}H_{23}NO_3$) C, H, N.

***trans*-1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic Acid (14).** Hydrolysis of 12b as described for 12a above afforded acid 14, mp 171–173 °C: NMR ($CDCl_3$) δ 8.48 (s, 1 H), 7.39–7.01 (m, 9 H), 3.90 (dd, 2 H, J = 7.5 Hz, J = 2.5 Hz), 3.19 (m, 2 H), 3.02 (d, 2 H, J = 3 Hz), 2.88 (m, 2 H), 2.15 (m, 2 H), 0.89 (t, 3 H, J = 7.5 Hz); IR (KBr) 3390, 1722 cm^{-1}. Anal. ($C_{22}H_{23}NO_3$) C, H, N.

Ethyl 3-Indoleglyoxalate Oxime (16). To ethyl 3-indoleglyoxalate (18.7 g, 0.086 mol) in EtOH (250 mL) were added NaOAc (53 g, 0.645 mol) in 120 mL of H_2O and NH_2OH·HCl (64.5 g, 0.645 mol) in 120 mL of H_2O. The mixture was refluxed for 5 h and left overnight at room temperature. The EtOH was evaporated, and the aqueous part extracted with EtOAc. The organic phase was washed with H_2O, dried over $MgSO_4$, treated with charcoal, and evaporated. The residue was triturated with ether to give the crystalline product (95%), mp 152–155 °C. Anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

α-Aminoindole-3-acetic Acid Ethyl Ester (17). To oxime 16 (2.2 g, 0.0095 mol) dissolved in 25 mL of EtOH were added concentrated HCl (3 mL) and 0.5 g of 5% Pd/C, and the mixture was hydrogenated under 40 psi at room temperature for 4 h. The catalyst was filtered off, and the solvent was evaporated. The residue was taken into H_2O and extracted with EtOAc. The acidic aqueous phase was basified with 20% NaOH solution and extracted with EtOAc. The organic phase was dried over $MgSO_4$, treated with charcoal, and concentrated to a solid (1.78 g). Trituration with ether provided 17 (80%), mp 103–104 °C. Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

β-Aminoindole-3-ethanol (18). Ester 17 (8.8 g, 0.04 mol) in 100 mL of THF was added dropwise under N_2 to $LiAlH_4$ (4.6 g, 0.12 mol) in 50 mL of THF, and the mixture was refluxed for 2 h. The excess hydride was destroyed with a mixture of THF–H_2O, and the inorganic salts were filtered off. The THF was evaporated, and the aqueous part was extracted with EtOAc. The extract was dried over $MgSO_4$, treated with charcoal, and evaporated to give a solid. The solid was triturated with acetone to afford 18 (90%), mp 133–135 °C dec. Anal. ($C_{10}H_{12}N_2O$) C, H, N.

β-Amino-*O*,*N*-diformylindole-3-ethanol (19). β-Aminoindole-3-ethanol (18) (28 g, 0.16 mol) and formic acetic anhydride from 213 mL of acetic anhydride and 90 mL of formic acid (88%) were combined and kept at room temperature for 18 h. The mixture was poured onto ice and water and extracted with EtOAc (3 × 200 mL). The combined EtOAc layer was washed carefully with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo to give 35 g of crude 19 (94%). This material was sufficiently pure for use in the next reaction: NMR ($CDCl_3$)

δ 4.6 (m, 2 H), 5.8 (m, 1 H), 7.0–7.8 (m, 5 H), 8–8.5 (m, 4 H).

β-Formamidoindole-3-ethanol (20). Compound **19** (35 g, 0.15 mol), methanol (200 mL), and a 5% solution of K_2CO_3 (200 mL) were heated at reflux for 2 h. The reaction was then cooled to room temperature extracted with EtOAc (3 × 200 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield 30 g (98%) of the product: NMR (DMSO-d_6) δ 3.4 (m, 2 H), 5.1 (m, 1 H), 6.6–8.2 (m, 6 H), 10.8 (s, 1 H).

1-Ethyl-4-formamido-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid Methyl Ester (21). A mixture of **20** (5 g, 0.024 mol) and methyl 3-methoxy-2-pentenoate (30 mL) in methylene chloride (200 mL) was treated slowly with 1 mL of $BF_3{\cdot}Et_2O$ and stirred for 16 h. The crude mixture was then filtered through a pad of silica gel, eluting with hexane–ether–EtOAc (2:2:1) to provide 5 g (64%) of **21** as an oil: NMR ($CDCl_3$) δ 0.8 (2 t, 3 H), 2.0 (m, 2 H), 2.8–3.2 (m, 2 H), 3.8 (2 s, 3 H), 4.1 (m, 2 H), 5.4 (m, 1 H), 5.8–6.3 (m, 1 H), 7–7.6 (m, 4 H), 8.2 (s, 1 H), 9.2 (s, 1 H).

4-Amino-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid Methyl Ester (22). A solution of **21** (7 g, 0.022 mol) in 30 mL of methanol was added to 30 mL of 1 N methanolic HCl. After 24 h at 25 °C, the solution was concentrated in vacuo and made alkaline with 20% NaOH. The free amine was extracted (3 × 200 mL) with EtOAc, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 6 g (97%) of **22** of sufficient purity to be used in the next reaction: NMR ($CDCl_3$) δ 0.85 (2 t, 3 H), 2.0 (m, 5 H), 2.8–3.2 (m, 2 H), 3.8 (2 s, 3 H), 4.1 (m, 2 H), 7–7.8 (m, 4 H), 8.8–9.2 (2 s, 1 H).

1-Ethyl-4-hydroxy-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid Methyl Ester (23). To a solution of amine **22** (6 g, 0.020 mol) in 50 mL of THF was added 50 mL of H_2O and paraformaldehyde (5 g), and the mixture was heated at reflux for 2 h under nitrogen. After the mixture was cooled and concentrated in vacuo, EtOAc was added. The mixture was washed with saturated sodium bicarbonate solution, and then with brine. The EtOAc solution was dried and concentrated in vacuo. Flash chromatography, eluting with hexane, afforded 4 g (66%) of **23**: NMR ($CDCl_3$) δ 0.9 (2 t, 3 H), 1.5 (s), 1.8–2.2 (m, 3 H), 2.8–3.1 (m, 2 H), 3.8 (2 s, 3 H), 4 (m, 2 H), 4.8 (m, 1 H), 7–7.7 (m, 4 H), 9–9.2 (2 s, 1 H).

1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic Acid Methyl Ester (12). Via Alternate Synthesis. To a solution of **23** (1 g, 0.0036 mol) in 60 mL of dry methylene chloride at −78 °C under nitrogen was added $TiCl_4$ (1.12 g, 0.0059 mol) followed by a solution of 1 M benzyl magnesium bromide in ether (3.9 mL, 0.0039 mol) after 10 min, and the reaction mixture was allowed to stir at −78 °C for 30 min. The reaction was quenched with MeOH (3 mL) at −78 °C and then poured into water (10 mL). Two layers were separated, and the aqueous layer was then extracted with methylene chloride (2 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was passed through a pad of silica gel, eluting with 9:1 hexane–EtOAc, to give 0.67 g of ester **12** (51%) with a diastereomeric ratio of 3:1 in favor of **12a** (HPLC analysis). Hydrolysis and two crystallizations gave pemedolac (>99% isomeric excess by HPLC analysis of its methyl ester).

Resolution of Pemedolac. The resolution of pemedolac (**13**) was carried out by the method described in detail for etodolac in ref 5. Crystals of (+)-pemedolac (*S*)-(−)-borneol ester, mp 123–125 °C, were grown from *n*-heptane for X-ray crystallography. Anal. ($C_{32}H_{39}NO_3$) C, H, N.

Hydrolysis of (+)-pemedolac (*S*)-(−)-borneol ester afforded **(+)-pemedolac (13a)**: mp 170–171.5 °C, $[a]_{25}^{D}$ +62.9° (2-propanol). Anal. ($C_{22}H_{23}NO_3$) C, H, N. Hydrolysis of (−)-pemedolac (*S*)-(−)-borneol ester afforded **(−)-pemedolac (13b)**: mp 171–172 °C; $[\alpha]_{25}^{D}$ −60.3° (2-propanol). Anal. ($C_{22}H_{23}NO_3$) C, H, N. Enantiomeric purities of better than 99.5% for both enantiomers were determined by HPLC analysis of the methyl esters with a chiral column.

Single-Crystal X-ray Analysis of (±)-Pemedolac. A colorless single crystal of $C_{22}H_{23}NO_3$ grown from toluene measuring 0.20 × 0.20 × 0.30 mm was mounted on a glass fiber and centered on a Nicolet R3m diffractometer. Cell constants and their esd's were determined by a least-squares fit of 15 diffractometer-measured reflections with 40° ≤ 2θ ≤ 45°. The material belonged to the orthorhombic crystal class with a = 6.271 (2) Å, b = 11.665 (4) Å, and c = 25.289 (5) Å. The systematic absences ($h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$) uniquely identified the space group to be $P2_12_12_1$ (No. 19). A density of 1.25 g/cm^3 was calculated for Z = 4, MW = 349.5 g, and a unit cell volume of 1850 (1) Å^3.

All intensity measurements with 3° ≤ 2θ ≤ 110° were made at room temperature with use of graphite-monochromated Cu Kα radiation (λ = 1.54178 Å) and an ω-scan technique with a variable scan rate of 3.91–29.30°/min. Background counts were taken for half the scan time at each extreme of the scan range. Two standard reflections, monitored after every 50 data measurements, showed a random 4% variation in intensity. The intensities were reduced by applying Lorentz and polarization corrections. Empirical absorption corrections were not applied. Of the 1411 unique reflections measured, 1331 were considered to be observed [$|F_o| > 3\sigma(F_o)$].

The structure was solved by direct methods by using the SHELXTL software.[9] All hydrogen atoms except the carboxyl hydrogen were located on difference Fourier maps following refinement of the non-hydrogen atoms. The hydrogen positions on carbon were subsequently idealized with C–H = 0.96 Å and $B(H) = 1.2 \times B(C)$. In the final cycles of blocked-cascade least-squares refinement, all non-hydrogen atoms were varied with anisotropic temperature factors; the NH hydrogen was held fixed, and a riding model was used for the remaining hydrogens. Final refinement with 236 parameters converged at R = 0.048 and R_w = 0.046 with goodness of fit = 4.30.[10] The largest peak in the final difference Fourier was 0.23 e/Å^3. Figure 1 is a labeled ORTEP drawing of the final crystallographic model.

Single-Crystal X-ray Analysis of (+)-Pemedolac (*S*)-(−)-Borneol Ester. A single crystal of $C_{32}H_{39}NO_3$ measuring 0.20 × 0.25 × 0.40 mm was mounted on a glass fiber and centered on a Nicolet R3m diffractometer. Cell constants and their esd's were determined by a least-squares fit of 25 diffractometer-measured reflections with 40° ≤ 2θ ≤ 45°. The material belongs to the orthorhombic crystal class, space group $P2_12_12_1$, with a = 8.585 (2) Å, b = 15.885 (3) Å, and c = 20.340 (4) Å. A density of 1.16 g/cm^3 was calculated for Z = 4, FW = 485.7 g, and a unit cell volume of 2773.7 (9) Å^3.

All intensity measurements were made at room temperature with graphite-monochromated Cu Kα radiation (λ = 1.5417 Å) and an ω-scan technique with a variable scan rate of 3.91–29.30°/min. Background counts were taken for half the scan time at each extreme of the scan range. All data (2178) having $h,k,l \geq 0$ with 3° ≤ 2θ ≤ 114° were measured in this manner. Crystal decomposition was monitored throughout data collection by remeasuring two standard reflections after every 50 data measurements; no large variations in intensity were recorded. The intensities were reduced by applying Lorentz and polarization corrections. Systematic absences were removed to give 2153 unique data of which 2027 were considered to be observed [$|F_o| > 3\sigma(F_o)$].

The structure was solved by direct methods with the SHELXTL software.[9] Following refinement of the non-hydrogen atoms with anisotropic temperature factors, difference Fourier maps showed plausible peaks for all 39 hydrogen atoms. The NH hydrogen was fixed; all other hydrogen atoms were subsequently included in refinement in ideal positions (C–H 0.96 Å, CCH 120° or 109°). In the final cycles of blocked-cascade least-squares refinement, the non-hydrogen atoms were refined with anisotropic temperature factors, and the hydrogens were varied with a riding model. Refinement converged (shift/error ≤ 0.15) at R = 0.043, R_w = 0.049. No peaks of consequence were present in a final difference map (maximum e/Å^3 = 0.21). Figure 2 is a labeled ORTEP drawing (with anisotropic thermal elliposoids).

Pharmacology Methods. 1. Phenylbenzoquinone Writhing Assay. Analgesic activity was determined in male Swiss albino mice (15–25 g) by a modification of the method of Siegmund et al.[11] Groups of 10 fasted mice received either the test com-

(9) SHELXTL software from Nicholet X-ray Instruments, P.O. Box 4370, Madison, WI 53711.

(10) $R = \sum||F_o| - |F_c||/\sum|F_o|$. $R_w = \sum[w(|F_o| - |F_c|)^2]^{1/2}/\sum(w|F_o|^2)^{1/2}$. GOF = $[\sum w(|F_o| - |F_c|)^2/(N_o - N_p)]^{1/2}$.

(11) Siegmund, E.; Cadmus, R.; Lu, G. *Proc. Soc. Exp. Biol. Med.* **1975**, *95*, 729.

pound or 0.5% Tween 80 vehicle by gastric gavage at 60 min prior to the intraperitoneal injection of PBQ (0.15 mL of a 0.02% solution/10 g body weight). The number of writhes made by each group of mice was determined for 15 min after the PBQ injection. The percent inhibition of writhing was calculated relative to the vehicle control group, and the ED_{50} and its 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[12]

2. **Randall–Selitto Paw Pressure Assay.** Analgesic activity was measured in the inflamed rat hindpaw by a modification of the method of Randall and Selitto.[13] Groups of 10 male Sprague–Dawley rats (180–200 g) received an intraplanar injection of 0.1 mL of Freund's Complete Adjuvant (5 mg dead and dried *Mycobacterium butyricum* in 1 mL of mineral oil) into the left hindpaw. Test compound or vehicle was administered 24 h thereafter by gastric gavage, and the pain threshold was determined 1 h later with a paw pressure apparatus (Ugo Basile, Comeria, Italy). Animals were defined as having an analgesic effect if their pain threshold was at least 50% greater than the mean of the vehicle-treated group. The ED_{50} and its 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[12]

3. **Carrageenan Paw Edema.** Acute antiinflammatory activity was determined according to the method of Winter et al.[14] Test compounds were administered by gastric gavage at 1 h prior to the intraplanar injection of 2% carrageenan in 0.9% saline into the left hindpaw. The acute edema volume was determined as the difference in hindpaw volume measured at the time of carrageenan injection and 3 h after carrageenan. The percent inhibition of edema formation was determined relative to the vehicle-treated controls, and the ED_{50} and its 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[12]

4. **Ulcerogenesis Assay.** Male Sprague–Dawley rats (180–200 g), fasted for 8 h, were administered a single dose of test compound by gastric gavage. Food was withheld, but the animals were allowed free access to water. Stomachs were assessed for the presence or absence of a lesion on a quantal basis at 18 h after test compound administration. The UD_{50} (dose of drug causing lesions in 50% of the animals) and its 95% confidence limits were calculated by the method of Litchfield and Wilcoxon.[12]

Registry No. 1, 91-56-5; **2**, 103-25-3; (±)-**3** (isomer 1), 113996-90-0; (±)-4, 113975-69-2; **5**, 1912-33-0; (±)-**6**, 113975-70-5; **7**, 87-51-4; (±)-**8**, 113975-71-6; **11**, 104065-67-0; (±)-**12a**, 113975-73-8; (±)-**12b**, 113975-83-0; (±)-**13**, 103024-44-8; **13a**, 114030-44-3; **13a** ((−)-borneol ester), 114030-43-2; **13b**, 114030-45-4; (±)-**14**, 113975-74-9; **15**, 18372-22-0; **16**, 113975-75-0; (±)-**17**, 113975-76-1; (±)-**18**, 113975-77-2; (±)-**19**, 113975-78-3; (±)-**20**, 113975-79-4; (±)-*cis*-**21**, 113975-80-7; (±)-*trans*-**21**, 113975-84-1; (±)-*cis*-**22**, 113975-81-8; (±)-*trans*-**22**, 113975-85-2; (±)-*cis*-**23**, 113975-82-9; (±)-*trans*-**23l**, 113975-86-3; $EtCOCH_2CO_2Me$, 3044-53-9; tryptophol, 526-55-6.

Supplementary Material Available: Listings of bond lengths, bond angles, atomic coordinates, and thermal parameters for (±)-pemedolac and (+)-pemedolac (*S*)-(−)-borneol ester (16 pages); tables of observed and calculated structure factors for (±)-pemedolac and (+)-pemedolac (*S*)-(−)-borneol ester (20 pages). Ordering information is given on any current masthead page.

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(15) Computer generated by using the SYBYL software package, version 3.4, Tripos Associates, St. Louis, MO.

An Intensely Sweet Dihydroflavonol Derivative Based on a Natural Product Lead Compound[1]

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The dihydroflavonol dihydroquercetin 3-acetate (1) was isolated as a sweet constituent of the young shoots of *Tessaria dodoneifolia* (Hook. & Arn.) Cabrera (Compositae). Compound 1 and dihydroquercetin 3-acetate 4'-(methyl ether) (**2**), a novel synthetic analogue of this natural product lead compound, were rated by a taste panel as being 80 and 400 times sweeter than a 2% w/v sucrose solution, respectively. Synthetic dihydroquercetin 4'-(methyl ether) (3) showed a reduced sweetness intensity when compared to **2**, while (+)-dihydroquercetin (4) was devoid of sweetness. Dihydroflavonol derivatives 1–3 represent a new class of potentially noncaloric and noncariogenic intense sweeteners.

As part of our continuing search for intensely sweet compounds of plant origin, we have investigated *Tessaria dodoneifolia* (Hook. & Arn.) Cabrera (family Compositae). This herb was obtained in a medicinal plants market in Asunción, Paraguay, where it was sold as a native remedy under the name "kaá hê-ê" (sweet herb). The young shoots of this plant were collected from a cultivated stand of *T. dodoneifolia*, and the sweetness was traced to an ethyl acetate soluble constituent, dihydroquercetin 3-acetate (1). Compound 1 was isolated initially from this plant source[2] and subsequently from two other plant species,[3] although its sweet taste had not been recognized previously. However, preliminary stability studies showed that this compound underwent slow spontaneous oxidation in neutral and basic media. This poor stability profile would render this compound unacceptable for use as a sweetener in foods, beverages, or medicines.

The structural similarity of 1 to intense sweeteners in the dihydrochalcone[4] and dihydroisocoumarin[5] classes

(1) Part 13 in the series Potential Sweetening Agents of Plant Origin. For part 12, see: Compadre, C. M.; Hussain, R. A.; Nanayakkara, N. P. D.; Pezzuto, J. M.; Kinghorn, A. D. *Biomed. Environ. Mass Spectrom.*, **1988**, *15*, 211.
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