Deoxybenzil (0.50 g, 0.0025 mol), TeO_3 (1.2 g, 0.0068 mol), and LiBr (1.2 g, 0.0138 mol) similarly afforded benzil (0.34 g) and benzoin acetate (0.11 g).

Benzoin acetate (1.0 g, 0.0039 mol), TeO_2 (1.5 g, 0.0094 mol), and LiBr (2.0 g, 0.023 mol) gave, after 24 h, benzil (0.63 g) and benzoin acetate (0.20 g).

Phenylacetic acid (1.0 g, 0.0074 mol), TeO_2 (1.5 g, 0.0094 mol), and LiBr (2.0 g, 0.023 mol) were heated at reflux for 29 h. The residue obtained after solvent evaporation was dissolved in $NaHCO_3$ (5% aqueous solution) and extracted with ether. Acidification (HCl) of the aqueous layer afforded the free acidic products which were extracted into ethyl ether. Methylation with diazomethane and chromatography afforded methyl mandelate acetate (0.55 g) and methyl phenylacetate (0.50 g). Both compounds were compared with authentic samples. When the experiment was carried out in a mixture of acetic anhydride (35 mL) and acetic acid (15 mL), diphenylmaleic anhydride (11) could be isolated in 5% yield from the first ether extract.

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Registry No. 1, 1335-47-3; 4, 733-07-3; 5, 63548-92-5; 9, 17472-04-7; 10, 5438-68-6; 12, 451-40-1; 13, 574-06-1; 14, 134-81-6; TeO_2, 7446-07-3; $Te(OH)_6$, 7803-68-1; TeO_3, 13451-18-8; LiBr, 7550-35-8; SeO_2, 7446-08-4; acetic acid, 64-19-7; acetoxycarbene, 83585-70-0; bromide anion, 24959-67-9; benzene, 71-43-2; toluene, 108-88-3; *o*-xylene, 95-47-6; *p*-xylene, 106-42-3; mesitylene, 108-67-8; benzyl acetate, 140-11-4; methylbenzyl acetate, 30676-70-1; dimethylbenzyl acetate, 83585-71-1; 2,5-dimethylbenzyl acetate, 22184-23-2; *m*-xylene, 108-38-3; 4-bromotoluene, 106-38-7; diphenylmethane, 101-81-5; triphenylmethane, 519-73-3; 4-methoxytoluene, 104-93-8; 2-methylnaphthalene, 91-57-6; 2-methylbenzyl acetate, 17373-93-2; 2-methylbenzaldehyde, 529-20-4; bromotoluene, 28807-97-8; 3-methylbenzyl acetate, 17369-57-2; 3-methylbenzaldehyde, 620-23-5; bromo-*m*-xylene, 42715-80-0; bromo-*o*-xylene, 51317-35-2; 4-methylbenzyl acetate, 2216-45-7; 4-methylbenzaldehyde, 104-87-0; bromo-*p*-xylene, 553-94-6; 4-bromobenzyl acetate, 21388-92-1; 4-bromobenzaldehyde, 1122-91-4; diphenylmethanol acetate, 954-67-6; benzophenone, 119-61-9; triphenylmethanol, 76-84-6; phenylacetic acid, 103-82-2; cyclohexanone, 108-94-1; *o*-methylbenzoic acid, 118-90-1; *o,p*-ditolylmethane, 21895-17-0; *p*-tolylmagnesium bromide, 4294-57-9; *o*-methylbenzaldehyde, 529-20-4; *o,p*-ditolylmethanol, 21945-70-0; acetic anhydride, 108-24-7; methylene diacetate, 628-51-3; bromomethyl acetate, 590-97-6; *m*-methylbenzoic acid, 99-04-7; *p*-methylbenzoic acid, 99-94-5.

Notes

Epoxidation of an Unsaturated Tertiary Amine. Application to the Synthesis of Two Pirprofen Metabolites

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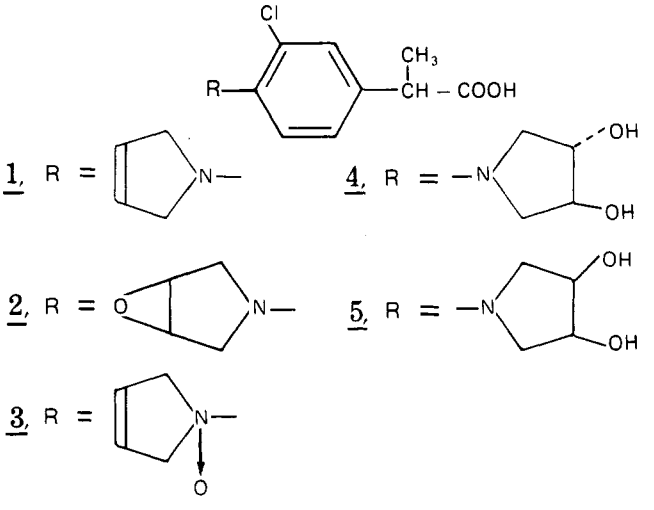
Pirprofen, 2-[3-chloro-4-(3-pyrrolin-1-yl)phenyl]-propionic acid (1, Chart I) is a new antiinflammatory agent.[1-3] Egger et al.[4] studied its in vivo metabolism and isolated several metabolites. One of the metabolites, A, was assigned the epoxide structure 2 and another metabolite, B, a dihydrodiol structure based on ^1H NMR and mass spectral characteristics. We undertook the unequivocal synthesis of these two metabolites to confirm their assigned structures, establish the stereochemistry of B, and also to prepare them on a larger scale for further biological studies. We report in this article that we have now synthesized the epoxide 2 by a novel method and found it to be identical with the isolated metabolite A. We have also synthesized two diols, 4 and 5 by unequivocal methods and found that the *trans*-diol 4 was identical with the metabolite B.

Epoxides are usually prepared by the electrophilic addition of an oxygen atom derived from an organic peracid to an olefinic double bond. The nucleophilic nitrogen of

Chart I



pirprofen posed a problem in the synthesis of the epoxide 2 by this method. Reaction of pirprofen with 1 mol equiv of peroxyacetic, peroxyformic, or 3-chloroperoxybenzoic acid gave a solid (mp 146–48 °C) which analyzed for a monooxide of pirprofen; its ^1H NMR spectrum showed bands due to olefinic protons. We therefore assigned the *N*-oxide structure 3 to this compound based on its ^1H NMR and mass spectral characteristics (Table I). In agreement with the structure 3, the ^1H NMR spectrum of the peracid oxidation product exhibited a peak at 5.97 ppm due to the olefinic protons. The methylene protons adjacent to the *N*-oxide moiety were shifted downfield to 4.97–5.09 ppm compared to the methylene protons of pirprofen, which appeared as a singlet at 4.3 ppm. One of the aromatic protons that is in close proximity to the *N*-oxide moiety was also shifted downfield to 8.5 ppm compared to the corresponding proton of pirprofen, which

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(2) Proctor, J. D.; Evans, E. F.; Velandia, J.; Wasserman, A. J. *Clin. Pharmacol. Ther.* **1983**, *14*, 143.
(3) Proctor, J. D.; Evans, E. F.; Campos, V.; Velandia, J.; Pollock, D.; Wingfield, W. L.; Wasserman, A. J. *Clin. Pharmacol. Ther.* **1974**, *16*, 69.
(4) Egger, H.; Bartlett, F.; Yuan, H.-P.; Karliner, J. *Drug Metab. Disp.*, in press.

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Table I

compound	mass spectrum *m/e* (rel intensity)	^{1}H NMR chem shifts, δ
pirprofen (1)	251 (M^+, 75), 206 (M^+ – COOH, 100)	1.41 (d, CH_3), 3.8 (q, CH), 4.3 (s, CH_2NCH_2), 5.78 (CH=CH), 6.7, 7.05, 7.2 (Ar H)
epoxide (2)	267 (M^+, 72), 249 (M^+ – H_2O, 10), 222 (M^+ – COOH, 100)	1.45 (d, CH_3), 3.6 (q, CH), 3.35, 3.88 (dd, CH_2NCH_2), 3.75 (s, CHOCH), 6.8, 7.05, 7.22 (Ar H)
N-Oxide (3)	267 (M^+, 5) 265 (M^+ – 2H, 3), 249 (265 – O, 100), 204 (249 – COOH, 90)	1.44 (d, CH_3), 3.6 (q, CH), 4.97-5.09[a] (m, CH_2NCH_2), 5.97 (CH=CH), 7.32, 7.40, 8.5 (Ar H)

[a] These peaks were resolved in dimethyl-d_6 sulfoxide solution to give two distinct AB doublets.

appeared as a doublet at 6.7 ppm. We then tried to oxygenate both the nitrogen atom and the double bond by treatment of pirprofen with a large excess of 3-chloroperoxybenzoic acid in the hope that the initial N-oxidation would be followed by epoxidation and the resulting *N*-oxy epoxide could then be selectively N-deoxygenated to give the epoxide **2**. However, the reaction of **1** with 10 mol equiv of 3-chloroperoxybenzoic acid for a week did not yield any *N*-oxy epoxide. A similar observation has been made by Fodor,[5] who found that when tropenol was treated with 20 mol equiv of monoperoxyphthalic acid, the corresponding *N*-oxy epoxide was formed only in a very low yield after a month.

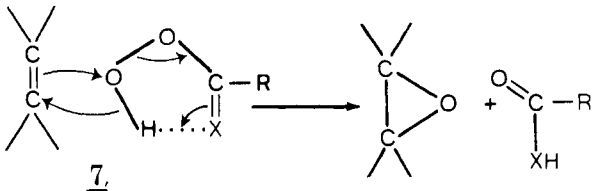
We then looked for an oxygenating agent that could be used under nonacidic condition to mimic the in vivo epoxidation. The nitrogen analogue of an organic peracid RC(=NH)OOH (**6**) seemed to be such a reagent. Peroxycarboximidic acids **6a** (**6**, R = CH_3) and **6b** (**6**, R = C_6H_5) have been prepared in situ (eq 1)by the base-catalyzed addition of hydrogen peroxide to acetonitrile and benzonitrile, respectively, and used for epoxidation of olefinic double bonds under slightly basic conditions by Payne and co-workers.[6] Accordingly, we treated the methyl ester of pirprofen in methanol solution with hydrogen peroxide and acetonitrile in the presence of potassium bicarbonate (to maintain a pH of 7.5–8) and isolated a monooxygenated derivative (55% yield) which was then hydrolyzed at room temperature by treatment with dilute sodium hydroxide solution to give a solid (mp 94–96 °C). It analyzed for a monooxide of pirprofen, but it was different from the *N*-oxide **3**. We assigned the epoxide structure **2** to it by comparison of its ^{1}H NMR chemical shifts and mass spectrum with those of pirprofen and the *N*-oxide **3** (Table I).

$$R{-}C{\equiv}N \xrightarrow{^-OOH} R{-}C(=N^-)OOH \rightarrow R{-}C(=NH)OOH \quad (1)$$

The ^{1}H NMR spectrum of the peroxycarboximidic acid oxidation product showed the absence of olefinic protons. Instead, it showed a peak at 3.75 ppm, which may be assigned to the protons of the oxirane ring. The protons of the two methylene groups adjacent to the nitrogen atom showed two equivalent doublets of doublets centered at 3.35 and 3.88 ppm. These results are in agreement with the structure **2**. The mass spectral fragmentation results are also consistent with the assigned structures. The base peak of the *N*-oxide (*m/e* 249) was formed by the loss of two hydrogen atoms and an oxygen atom, whereas the base peak (*m/e* 222) of the epoxide was formed by the loss of the carboxyl group as in the case of pirprofen (*m/e* 206) itself. The peak at *m/e* 249 of the epoxide was very small.

The epoxide **2** was hydrolyzed by heating with 2 N sodium hydroxide solution until a diol was formed. Since the base hydrolysis of an epoxide takes place by an S_N2 mechanism, the resultant diol must be a mixture of diastereoisomers having a trans configuration represented by the structure **4**. The *cis*-diol **5** was prepared by oxidation of pirprofen with osmium tetraoxide. It was a crystalline solid in contrast to the *trans*-diol, which was a low-melting amorphous solid. Although the ^{1}H NMR spectra of the diols **4** and **5** were somewhat alike, some differences could be discerned. The chemical shift for the hydrogens linked to the carbon atoms bearing the hydroxyl groups was 4.25 ppm for the *cis*-diol **5** and 4.15 ppm for the *trans*-diol **4**. The methyl esters of **4** and **5** also exhibited similar differences. The hydrogens of the methyl group (CH_3CH) in the side chain of the two methyl esters had the same chemical shift (1.43 ppm), but the remaining aliphatic hydrogens of the cis ester were found in a narrower chemical shift range (between 3.25 and 3.68 ppm) compared to the range (between 3.2 and 3.78 ppm) of the trans ester. The two esters behaved differently on thin-layer chromatography and high-pressure liquid chromatography. Metabolite B and its methyl ester were found to be identical with the *trans*-diol **4** and its methyl ester, respectively, according to their ^{1}H NMR and mass spectra.

The epoxidation of olefins by peracids is believed to proceed by an electrophilic attack of the double bond by the peracid as shown in **7** (X = O),[7a] and an oxygen atom



7

is transferred from the peracid to the olefin. N-Oxidation of tertiary amines is believed to take place in an analogous manner.[7b] Although the mechanism of epoxidation with hydrogen peroxide–acetonitrile (or benzonitrile) system has not been rigorously established, it is generally believed that this oxidizing system involves a peroxycarboximidic acid[6] intermediate, and the mechanism of epoxidation (**7**, X = NH) is similar to the mechanism of epoxidation by peracids.

Although the oxidations with peracids and peroxycarboximidic acid systems are mechanistically similar, oxidation of pirprofen with these reagents took place regiospecifically at different sites. The preferential attack of the double bond instead of the nucleophilic nitrogen atom by peroxycarboximidic system can be explained by assuming that a peroxycarboximidic acid system has a greater steric bulk than peracids and therefore cannot attack the nitrogen atom of pirprofen, which is sterically more crowded than the double bond.

A similar explanation has been offered by Carlson and Behn[8] for the preferential equatorial attack of several

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(6) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659. Payne, G. B. *Tetrahedron* **1962**, *18*, 763.
(7) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin/Cummins: Menlo Park, CA; (a) p 302; (b) p 330.

methylenecyclohexane systems by peroxybenzimidic acid systems to give predominantly equatorial epoxides, in contrast to expoxidation by peracids, which gave predominantly products from an axial attack.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions at 90 MHz on a Varian Em 390 instrument. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard, and multiplicity of NMR signals are described as s = singlet, d = doublet, dd = doublet of doublets, q = quartet, and m = multiplet. Mass spectra were recorded on a AEI MS 902 instrument. Thin-layer chromatography (TLC) was performed on silica gel 60 F 254 plates (Merck) of 0.25 mm thickness and visualized under ultraviolet light. High-pressure liquid chromatography (HPLC) was performed on a DuPont Model 820 instrument.

***N*-Oxide of Pirprofen (3).** To a solution of 2.5 g of pirprofen in 10 mL of ethyl acetate was added 2 mL of 25% peroxyacetic acid solution in ethyl acetate, and the solution was stirred overnight at room temperature. The crystalline solid formed was filtered and recrystallized from a mixture of methanol and ether (1:5) to yield 2.3 g of a white solid: mp 146–48 °C dec; mass and ^{1}H NMR spectrum in Table I. Anal. Calcd for $C_{13}H_{14}O_3NCl$: C, 58.32; H, 5.23; N, 5.23. Found: C, 58.09; H, 5.51; N, 4.99.

2-[3-Chloro-4-(6-oxa-3-azabiocyclo[3.1.0]hex-3-yl)-phenyl]propionic Acid (2). A solution of 2.6 g of pirprofen in ether was treated with a solution of diazomethane in ether. After 30 min, ether was evaporated and the residue dissolved in 50 mL of methanol. To the methanol solution was then added 3.5 mL of acetonitrile, 4 mL of 30% H_2O_2 solution, and 1 g of potassium bicarbonate, and the mixture was stirred at room temperature for 2.5 h. Methanol was removed by evaporation under reduced pressure and the residue treated with water. The mixture was then extracted with ether, and the ether extract was dried ($MgSO_4$) and evaporated to give 2.5 g of a light yellow oil, which was then chromatographed on a column of silica gel. Elution with toluene removed the faster moving minor component (identified by ^{1}H NMR spectroscopy as the pyrrole analogue of pirprofen). The column was then eluted with ethyl acetate. Removal of ethyl acetate from the eluate gave 1.5 g of the methyl ester of **2** as a light yellow oil: ^{1}H NMR δ 1.41 (d, 3 H), 3.31, 3.85 (dd, 4 H), 3.60 (s, 3 H), 3.65 (m, 1 H), 3.70 (s, 2 H), 6.80 (d, 1 HO, 7.02 (m, 1 H), 7.20 (m, 1 H); mass spectrum, *m/e* (rel intensity) 281 (52), 263 (16), 222 (100), 204 (18). Anal. Calcd for $C_{14}H_{16}O_3NCl$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.62; H, 5.94; N, 4.88.

To 0.5 g of the above yellow oil was added 20 mL of 5% methanolic KOH solution, and the mixture was stirred at room temperature for 2 h. Methanol was removed and the residue dissolved in water. The aqueous solution was acidified (pH 5.5–6.0) and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated to give a light yellow oil, which was then chromatographed on a column of silica gel. Ethyl acetate eluate gave 0.3 g of the epoxy acid **2**, which was crystallized from a mixture of ether and cyclohexane (1:6); mp 94–96 °C;mass and ^{1}H NMR spectrum in Table I. Anal. Calcd for $C_{13}H_{14}O_3NCl$: C, 58.32; H, 5.23; H, 5.23. Found: C, 58.21; H, 5.29; N, 5.26.

2-[3-Chloro-4-(3,4-*trans*-dihydroxypyrrolidino)phenyl]-propionic Acid (4). The methyl ester of the epoxide **2** (3.5 g) was heated with 50 mL of 10% NaOH solution for 3 h under reflux. The solution was cooled, acidified (pH 4.5), and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to dryness to give an oily residue, which was then chromatographed on a column of silica gel. Elution with ether (which removed an impurity) was followed by elution with ethyl acetate. The ethyl acetate eluate on evaporation gave an oil, which became solid after drying in high vacuum. All attempts at crystallization failed. TLC in ethyl acetate showed one spot; mass spectrum *m/e* 285, 240, 225, 212, 197, and 180; ^{1}H NMR (Me_2SO-d_6) δ 1.42 (d, 3 H), 2.33 (s, 2 H), 3.21 (m, 2 H), 3.6 (q, 1 H), 3.8 (dd, 2 H), 4.15 (br, 2 H), 6.9 (d, 1 H), 7.2 (m, 1 H), 7.3 (d, 1 H). Anal. Calcd for $C_{13}H_{16}O_4NCl$: C, 54.64; H, 5.60; N, 4.90. Found: C, 54.84; H, 5.91; N, 4.64. The methyl ester of **4** was prepared by treatment of **4** with diazomethane and worked up in the usual way to give an oil; *m/e* (rel intensity) 299 (80), 240 (100), 226 (18), 211 (40); ^{1}H NMR 1.43 (d, 3 H), 3.1 (s, 2 H), 3.21 (dd, 2 H), 3.52 (q, 1 H), 3.65 (s, 3 H), 3.7 (dd, 2 H), 4.15 (br, 2 H), 6.73 (d, 1 H), 7.1 (m, 1 H), 7.2 (d, 1 H). Anal. Calcd for $C_{14}H_{18}O_4NCl$: C, 56,10; H, 6.01; N, 4.67. Found: C, 56.44; H, 6.35, N, 4.39.

2-[3-Chloro-4-(3,4-*cis*-dihydroxypyrrolidino)phenyl]-propionic Acid (5). To a solution of 2 g of pirprofen in 40 mL of ether were added 1 mL of pyridine and a solution of 2 g of osmium tetraoxide in 20 mL of ether, whereupon a brown precipitate was formed. The reaction mixture was diluted with 40 mL of ether and left overnight at room temperature. The brown solid was filtered and transferred to a 250-mL flask. Ethanol (50 mL) and a solution of 10 g of sodium sulfite in 50 mL of water were then added to the solid, and the mixture was heated under reflux for 5 h. The reaction mixture was cooled and filtered. The filtrate was concentrated to a small volume, acidified (pH 4.5–5.0), and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated to dryness. The residue was then stirred with ether and filtered. The filtrate was evaporated to dryness and the residue crystallized from a mixture of ether and benzene. The crystalline material on recrystallization from a mixture of ethyl acetate and petroleum ether gave 1.4 g of a white crystalline solid: mp 115–16 °C; mass spectrum, *m/e* 285, 240, 212, 197, 180; ^{1}H NMR (Me_2SO-d_6) δ 1.44 (d, 3 H), 3.3 (dd, 2 H), 3.5 (q, 1 H), 3.62 (dd, 2 H), 4.25 (m, 2 H), 6.75 (d, 1 H), 7.1 (m, 1 H), 7.22 (d, 1 H). Anal. Calcd for $C_{13}H_{16}O_4NCl$: C, 54.64; H, 5.60; N, 4.90. Found: C, 54.77; H, 5.42; N, 4.84. The methyl ester of **5** was prepared by treatment of **5** with diazomethane and worked up in the usual way to give an oil: *m/e* (rel intensity) 299 (80), 240 (100), 226 (20), 211 (45); ^{1}H NMR δ 1.43 (d, 3 H), 3.3 (dd, 2 H), 3.42–3.7 (m, 8 H), 4.25 (br, 2 H), 6.7 (d, 1 H), 7.1 (m, 1 H), 7.2 (d, 1 H). TLC of a mixture of **4** and **5** was run in ethyl acetate as well as in chloroform–methanol–formic acid system, where the *cis*-diol **5** moved slightly faster than the *trans*-diol **4**. HPLC of a mixture **1**, **2**, **4**, and **5** was performed on a Zorbax C_{18} column with retention times of 14, 9.6, 4.0, and 4.7 min, respectively, the solvent system being methanol–water–perchloric acid (55:45:0.2).

Acknowledgment. We are grateful to Dr. J. Karliner and his staff of the Corporate Research Department for the ^{1}H NMR and mass spectra and R. Luders for the HPLC.

Registry No. 1, 31793-07-4; 1 methyl ester, 59235-36-8; 2, 59235-33-5; 2 methyl ester, 82537-12-0; 3, 31796-82-4; 4 (isomer 1), 82537-09-5; 4 (isomer 2), 82537-10-8; 4 methyl ester, 82537-11-9; 5, 82570-90-9.

(8) Carlsen, R. G.; Behn, N. S. *J. Org. Chem.* **1967**, *32*, 1363.

Dianions of 2,5-Dimethyl-2,4-hexadiene. Evidence for the Stability of an 8-π-Electron Cross-Conjugated System

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Neutral linearly conjugated systems are generally recognized to possess greater stabilization than the isomeric cross-conjugated systems;[1] however, this tendency is frequently reversed in polyanionic systems.[2,3] We found, for

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(2) For purposes of the following discussion, dilithio- and dipotassioalkenes will be referred to as dianions with the understanding that there may be significant covalent character in the carbon–metal bond.

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