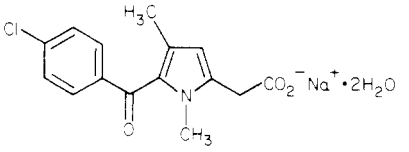
Synthesis and Biological Activity of 5-(4-Chlorobenzoyl)-4-(hydroxymethyl)-1-methyl-1*H*-pyrrole-2-acetic Acid, a Major Metabolite of Zomepirac Sodium

Neal G. Anderson and John R. Carson*

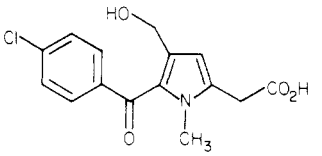
Chemical Research Department, McNeil Laboratories, Fort Washington, Pennsylvania 19034. *Received August 9, 1979*

5-(4-Chlorobenzoyl)-4-(hydroxymethyl)-1-methyl-1*H*-pyrrole-2-acetic acid (**2**), the major oxidative metabolite of zomepirac (**1**), was synthesized starting with ethyl 5-(4-chlorobenzoyl)-1,4-dimethyl-1*H*-pyrrole-2-acetate (**3**), the ethyl ester of **1**. Compound **3** was oxidized with selenium dioxide to afford the α-oxoester, **5**. Bromination of **5** with *N*-bromosuccinimide produced bromomethylpyrrole **7**, and reaction of **7** with acetate produced the corresponding acetoxymethylpyrrole **8**. Hydrogen sulfide effected the selective reduction of the side-chain carbonyl group of **8** to give **9**. Saponification of **9** gave the title compound, **2**. Synthetic **2** was identical with the isolated metabolite of zomepirac (**1**). Biological testing revealed that the metabolite was essentially devoid of the biological activity associated with zomepirac.

Zomepirac sodium (Zomax, **1**) is a new agent which has



1



2

shown pronounced analgesic activity in clinical trials.[1,2] This pyrroleacetic acid arose from our study of nonsteroidal antiinflammatory agents. The 4-(hydroxymethyl) compound (**2**) has been identified as the major metabolite in rats and a significant metabolite in man.[3] As part of the development of **1**, we undertook the synthesis of metabolite **2**.

Chemistry. A practical route for the preparation of **2** was not immediately apparent. The chemical properties of the pyrrole substituents discourage direct sequential introduction via substitution reactions. Hydroxymethylpyrroles tend to polymerize unless the pyrrole nucleus is deactivated by an electron-withdrawing substituent,[4] and thus the stability of intermediates could not be assured unless the hydroxymethyl group of **2** were introduced after benzoylation. Since 5-benzoyl-1-methylpyrrole-2-acetic acid derivatives undergo electrophilic substitution exclusively at the 3 position of the pyrrole,[5] it was clear that pyrrole substitution reactions would not be suitable for the preparation of **2**. We therefore directed our efforts toward selective oxidation of the 4-methyl substituent of **1** or its derivatives.

We examined two microorganisms which were known to effect selective oxidation of aromatic methyl groups. The incubation of **1** with either *Aspergillus sclerotiorum* or *Penicillium adametzi* under conditions which brought about oxidation of lucanthone or nalidixic acid,[6] respectively, produced no detectable **2**.

Attempts at conventional chemical oxidation of derivatives of **1** proved fruitless. Reaction of ester **3**[1] with *N*-bromosuccinimide (NBS) gave the nuclear bromo compound **4** in very good yield (see Scheme I). Further bromination of **4** gave complex mixtures, as did treatment of **3** with lead tetraacetate. Exposure of **1** or **3** to lithium diisopropylamide/oxygen, a combination known to effect oxygenation of anions adjacent to carboxylates,[7] also produced a complex mixture of products.

It seemed likely that the reactivities of the pyrrole ring and the α-methylene of the acetic ester side chain were higher than the reactivity of the 4-methyl group toward oxidizing agents. Therefore, we sought to selectively oxidize the α-methylene group to a carbonyl group, to protect the pyrrole ring and the α carbon of the side chain.

Treatment of **3** with selenium dioxide gave the oxoester **5**. The best results were obtained in pyridine with triethylamine added. If water was not scrupulously excluded, significant quantities of the corresponding alcohol **6** were obtained.[8] Reaction mixtures containing **6** could be fully oxidized to **5** by further reaction with manganese dioxide.

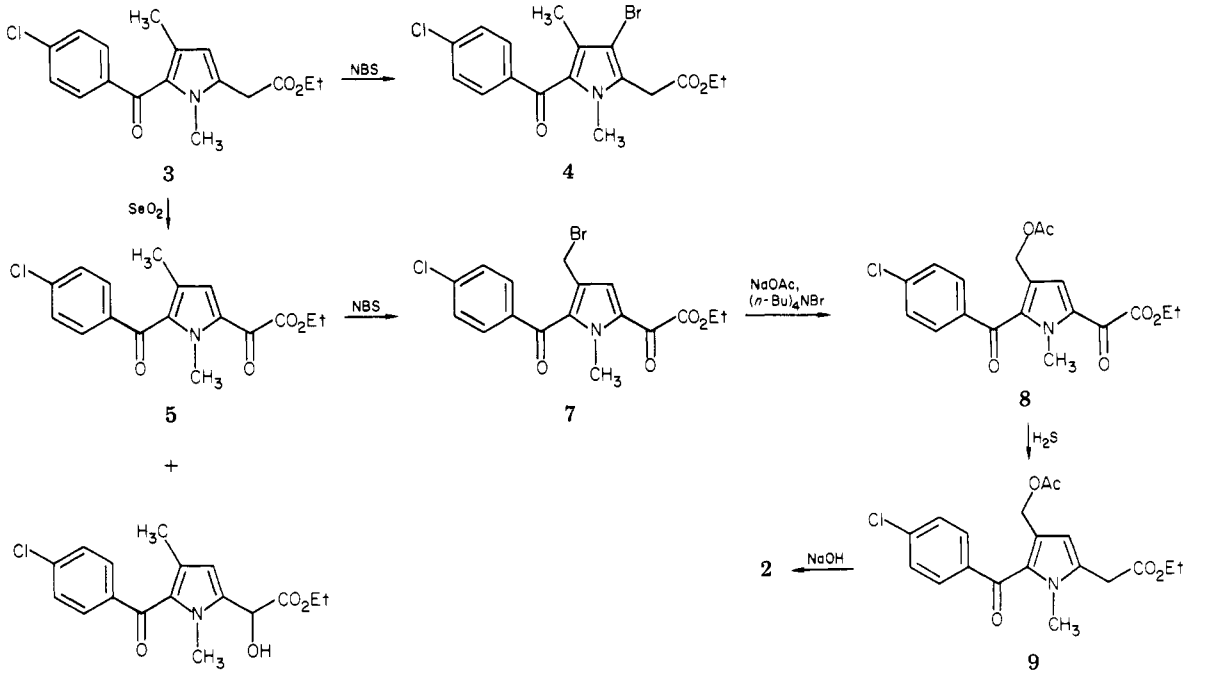
Bromination of **5** with NBS produced the bromomethyl compound **7** smoothly. Crude bromomethylpyrrole **7** was converted to the acetoxymethylpyrrole **8** through treatment with sodium acetate and tetrabutylammonium bromide.

The final problem posed by this sequence was selective reduction of the carbonyl group of the ester side chain of **8** in the presence of the benzoyl carbonyl group. We were attracted by the hydrogen sulfide method of Scheithauer and Mayer,[9] a system shown to reduce carbonyl groups adjacent to strong electron-withdrawing groups. Treatment of **8** with hydrogen sulfide in pyridine afforded the reduced acetoxy ester **9** in 63% yield. Finally, saponification of **9** gave **2**, isolated as the sodium salt. The free acid of synthetic **2** was identical with the metabolite isolated from rat urine.

(1) J. R. Carson and S. Wong, *J. Med. Chem.*, **16**, 172 (1973).
(2) S. Cooper and S. Gottlieb, *J. Dent. Res.*, **56**, A 140 (1977); S. A. Cooper and S. Gottlieb, *Clin. Pharmacol. Ther.*, **21**, 101 (1977).
(3) J. M. Grindel, P. J. O'Neill, K. A. Yorgey, J. E. Epps, M. Schwartz, L. E. Weaner, and B. H. Migdalof, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 691 (1978).
(4) R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles", Academic Press, New York, 1977, p 164.
(5) A. Gossauer, "Die Chemie der Pyrrole", Springer-Verlag, Berlin, 1974, p 120.
(6) D. Rosi, T. R. Lewis, R. Lorenz, H. Freele, D. A. Berberian, and S. Archer, *J. Med. Chem.*, **10**, 877 (1967); D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, M. Freele, B. F. Tullar, and S. Archer, *ibid.*, **10**, 867 (1967); P. B. Hamilton, D. Rosi, G. P. Peruzzotti, and E. D. Nielson, *Appl. Microbiol.*, **17**, 237 (1969). We thank Dr. F. C. Nachod of the Sterling-Winthrop Research Institute for generous samples of lucanthone and hycanthone.
(7) D. A. Konen, L. S. Silbert, and P. E. Pfeffer, *J. Org. Chem.*, **40**, 3253 (1975).
(8) F. Camps, J. Coll, and A. Parente, *Synthesis*, 215 (1978).
(9) M. Scheithauer and R. Mayer, *J. Prakt. Chem.*, **35**, 41 (1967); R. J. Carmosin, U.S. Patent 4125537 (1978).

0022-2623/80/1823-0098$01.00/0 © 1979 American Chemical Society

Scheme I



Pharmacology. The pharmacological profile of metabolite **2** was compared to that of zomepirac sodium (**1**). The metabolite was administered as its sodium salt.

In the rat adjuvant-induced polyarthritis (AA) test phase II and phase III[10] at doses up to 125 mg/kg po, **2** was inactive. The ED_{50} of zomepirac sodium is 0.72 (0.64–0.82) mg/kg in the phase II components and 5.67 (3.78–10.9) mg/kg in the phase III components of the AA test.

The analgesic activity of **2** was evaluated in the acetylcholine-induced body constriction assay.[10] At doses up to 100 mg/kg po, **2** was inactive. The ED_{50} of **1** in this test is 0.72 (0.49–1.10) mg/kg po.

The ability of **2** to inhibit the collagen-induced aggregation of human platelets in vitro was measured.[11] The IC_{50} of **2** is 529 ± 99 μM, while the IC_{50} of **1** is 1.63 ± 0.17 μM and that of indomethacin is 1.80 ± 0.12 μM.

At doses up to 100 mg/kg po in the rat, **2** was without ulcerogenic activity.[10] The UD_{50} of **1** is 13.9 (13.7–14.2) mg/kg.

Conclusion

The major metabolite **2** of zomepirac sodium in the rat is essentially devoid of the pharmacological activity associated with the parent compound. This observed loss of activity may be due to the decreased lipophilicity of the hydroxy metabolite. Similar metabolic hydroxylation of an alkyl group of ibuprofen has also been shown to abolish activity.[12] In conclusion, the activity of zomepirac sodium does not appear to involve metabolite **2**.

Experimental Section

Melting points were observed on a Thomas-Hoover Unimelt apparatus and are uncorrected. Physical chemical data were obtained on the following instruments: IR spectra, Perkin-Elmer 521 or Perkin-Elmer 283 spectrophotometers; NMR spectra, Perkin-Elmer R32 spectrometer; UV spectra, Cary 14 spectrophotometer; and mass spectra, Hitachi Perkin-Elmer RMU6 spectrometer. Microanalyses were performed by Scandinavian Laboratories, Herlev, Denmark. Reagent-grade pyridine and carbon tetrachloride were stored over 4Å sieves before use.

Ethyl 5-(4-Chlorobenzoyl)-1,4-dimethyl-1*H*-pyrrole-2-oxoacetate (5). To a mechanically stirred solution of 20.0 g (62.5 mmol) of ester **3** and 4.3 mL (31.3 mmol) of triethylamine in 100 mL of pyridine was added 7.60 g (68.7 mmol) of selenium dioxide. After the mixture was stirred under N_2 at 95–100 °C for 3.25 h, the black suspension was poured onto a bed of diatomaceous earth. The bed was washed with Et_2O, and the filtrate was washed with 2 N HCl. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with saturated $NaHCO_3$ and brine and then dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was recrystallized three times from absolute EtOH and once from 1:1 absolute EtOH–EtOAc to afford 14.2 g (64.3%) of yellow crystalline solid, mp 113.5–115.5 °C. This material was used as such in other reactions. Further recrystallization from absolute EtOH gave material with mp 115–116 °C. Anal. ($C_{17}H_{16}ClNO_4$) C, H, N.

Ethyl 4-[(Acetyloxy)methyl]-5-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrole-2-oxoacetate (8). A suspension of 34.82 g (0.104 mol) of **5** and 22.28 g (0.125 mol) of NBS (recrystallized from H_2O) in 300 mL of CCl_4 was irradiated at reflux under N_2 with a 150-W sunlamp. After 2.25 h, the reaction was cooled and the floating solid was filtered off and washed with 100 mL of CCl_4. The combined filtrates were refluxed 14.5 h under N_2 in the presence of 6.72 g (0.0209 mol) of $(n\text{-Bu})_4NBr$ and 25.66 g (0.312 mol) of anhydrous NaOAc. The flask was cooled and the solvent was removed at aspirator pressure. The resulting deep green residue was taken up into Et_2O and washed with 2 N HCl, saturated $NaHCO_3$, H_2O, and brine. After drying over Na_2SO_4, the solution was evaporated to afford a green solid. Recrystallization from Et_2O afforded 24.90 g of a cream-colored solid, mp 79.5–82.5 °C. This material was 95.6% pure by GC, the major contaminant being unreacted **5**, for a calculated yield of 58.5%. The crude acetate was used without further purification in the subsequent reduction. Two additional recrystallizations from Et_2O gave a cream-colored solid, mp 81.5–83 °C. Anal. ($C_{19}H_{18}ClNO_6$) C, H, N.

Ethyl 4-[(Acetyloxy)methyl]-5-(4-chlorobenzoyl)-1-methyl-1*H*-pyrrole-2-acetate (9). A solution of 20.77 g (95.4% pure, 50.57 mmol) of **8** and 7.22 g (106.1 mmol) of imidazole in

(10) S. Wong, J. F. Gardocki, and T. P. Pruss, *J. Pharmacol. Exp. Ther.*, **185**, 127 (1973).
(11) G. V. R. Born, *Nature (London)*, **194**, 927 (1962); H. Holmsen, A. Ostvold, and H. J. Day, *Biochem. Pharmacol.*, **22**, 2599 (1973).
(12) S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholson, *J. Pharm. Sci.*, **56**, 1686 (1967); S. S. Adams, K. F. McCullough, and J. S. Nicholson, *Arch. Int. Pharmacodyn. Ther.*, **178**, 115 (1969).

210 mL of pyridine was stirred under 40 psi of H_2S for 7.5 h. The deep red reaction was poured into 960 mL of 2 N HCl, and the filtrate was washed with 700- and 500-mL portions of Et_2O. The combined organic phases were washed with four portions of 10% Na_2CO_3 and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a sticky yellow solid, smelling strongly of H_2S, which was taken up into boiling $CHCl_3$. The resulting granular yellow precipitate was discarded, the filtrate was concentrated, and the residue was treated again in a similar manner. After removal of the second crop of sulfur, the filtrate was concentrated and the residue was recrystallized from $CHCl_3$ or Et_2O to give combined 16.21 g of an off-white solid. Recrystallization from Et_2O gave 12.71 g (63.4%) of fluffy, off-white needles, mp 102.5–103.5 °C. Anal. ($C_{19}H_{20}ClNO_5$) C, H, N.

5-(4-Chlorobenzoyl)-4-(hydroxymethyl)-1-methyl-1*H*-pyrrole-2-acetic Acid (2). To a solution of 5.96 g (15.8 mmol) of **9** in 70 mL of absolute EtOH at 75 °C was added a solution of 34.7 mL of 1.0 N NaOH (34.7 mmol). After 20 min, the reaction was cooled to room temperature, filtered, and cooled in a crushed ice bath to afford three crops of yellow platelets. These crops were combined and recrystallized from EtOH–H_2O to afford 4.53 g (71.3%) of light yellow flakes, melting range dependent on rate of heating. Anal. ($C_{15}H_{13}ClHO_4{\cdot}Na{\cdot}4H_2O$) C, H, N, H_2O. With shaking, 402 mg (1 mmol) of that salt was partitioned between 75 mL of 2 N HCl and 175 mL of 1:1 EtOAc–Et_2O. The organic phase was washed with brine and dried over Na_2SO_4. Solvents were removed under reduced pressure to give an orange solid, which was recrystallized three times from EtOAc to yield 115 mg (37%) of a light yellow solid, mp 169–169.5 °C. This material was identical with the isolated metabolite by NMR, UV, TLC, high-performance LC, IR, and MS: ^1H NMR (Me_2SO-d_6) δ 7.62 (d, 2 H, J = 9 Hz), 7.50 (d, 2 H, J = 9 Hz), 6.17 (s, 1 H), 4.65 (br hump, 1 H, exchangeable with D_2O), 3.88 (s, 2 H, sharpened by the addition of D_2O), 3.73 (s, 2 H), 3.62 (s, 3 H); IR (KBr) ν_{max} 3411, 2952, 1737 (br), 1607 cm^{-1}; MS m/e 309, 307 (100%); UV (CH_3CN) λ_{max} 254 nm (ϵ 1.28 × 10^4), 315 (1.12 × 10^4). Anal. ($C_{15}H_{14}ClNO_4$) C, H, N.

Acknowledgment. The authors thank Drs. T. P. Pruss, S. Wong, and J. F. Gardocki for pharmacological data, Dr. L. D. Muschek for biochemical data, and Dr. R. Gilpin for analytical data.

Book Reviews

Analytical Profiles of Drug Substances. Volume 7. Edited by K. Florey. Academic Press, New York. 1978. 15.5 × 22 cm. ix + 504 pp. $24.00.

The usefulness of this series to all pharmaceutical scientists and educators is well established. This seventh volume includes 18 detailed descriptions of drugs monographed in the official compendia: allopurinol, amoxicillin, chlorpheniramine maleate, dihydroergotoxine methanesulfonate, diphenoxylate hydrochloride, droperidol, epinephrine, ethambutol hydrochloride, fluoxymestrone, hexetidine, hydroflumethiazide, hydroxyzine dihydrochloride, 6-mercaptopurine, phenobarbital, sulfamethazine, thiostrepton, trimethoprim, and tubocurarine chloride.

More medicinally oriented chemists may be pleased to learn that a companion series covering the *Pharmacological and Biochemical Properties of Drug Substances*, the first volume of which is announced in the preface to this volume, will eventually create a truly encyclopedic work on our clinically useful drugs.

Staff

Mechanisms of Pain and Analgesic Compounds. Eleventh Miles International Symposium. Edited by F. Beers, Jr., and Edward G. Bassett. Raven Press, New York. 1979. xiii + 496 pp. 16 × 24 cm. $39.50.

The eleventh volume of the Miles International Symposium series is a collection of papers and the discussions which took place at the end of each of the sessions presented in Baltimore in June 1978. The symposium opened with a touching memorial tribute to the late Maurice Seevers presented by Dr. Walter Compton of Miles Laboratories.

The scientific part of the symposium is divided into six sections, the first of which deals mainly with current concepts of the nature of pain. The following section is comprised of a group of papers dealing with the neurophysiology of pain. Each of the contributions was written by an authority in this field, as is true for all of the other papers, but are primarily of interest to clinicians and neurophysiologists. The last four sections, which make up well over half the volume, are of greater interest to medicinal chemists.

The subject matter in the section entitled "Endogenous Substances Having Analgesic Action" is almost entirely limited to the enkephalins and endorphins—none of the newer opioid peptides, some of which were reported after this meeting was held, are discussed. The next section on peripheral mechanisms of pain and analgesics should be read by those engaged in research on nonopioid analgesics and antiinflammatory agents. The fifth section contains papers on the mode of action of opiates by such well-known investigators as Collier, Klee, North, and Herz.

The last section is entitled "New Leads for the Development of Analgesics". Even though the discussion leader, Julian Villareal, employed the term, "leads" in the sense that they are "presented as clues for action or objectives for focusing effort", this reviewer feels that the title of this section is misleading. Most if not all the material in this section is not new, and at least one reader does not feel that any new insights are presented to aid in designing new analgesics. Despite the misleading nature of the title, this section should prove to be quite useful to medicinal chemists in general and of particular interest to those engaged in analgesic research.

The organizers of the symposium and editors of the volume are to be congratulated for gathering a group of investigators whose papers were of uniformly high quality and for managing to publish them in a hard-cover book using conventional printing in so short a period of time.

Rensselaer Polytechnic Institute **Sydney Archer**

Progress in Drug Research. Volume 22. Edited by Ernst Jucker. Birkhäuser Verlag, Basel. 1978. 412 pp. 17 × 24.5 cm. $112.00.

Volume 22 contains eight contributions from various areas of drug research and therapy. Reviewed in this issue are "Aspects of Social Pharmacology" (by J. Venulet), "Fundamental Structure in Drug Research II" (by O. Schier and A. Marxer), "Antifungal Agents" (by P. F. D'Arcy and E. M. Scott), "Analgesics and their Antagonists: Recent Developments" (by A. F. Casy), "The Benzodiazepine Story" (by L. H. Sternbach), "Antiviral Agents" (by D. L. Swallow), "Clinical-Pharmacological Criteria in the Development of a New Antibiotic Basis and Methods" (in German) (by H. P. Kuemmerle), and "Drug Research and Human Sleep" (by I. Oswald). We call attention to the fact that this volume is the last which went into press during Dr. A. Birkhäuser's lifetime; he passed away on March 4, 1978. Dr. Birkhäuser founded this series of monographs and gave his strong support for the last 20 years. All in drug research are saddened by his passing and can think of no better memorial to him than the