7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, 125 ml of THF, and 45 ml of allyl isocyanate (added 25 ml at start and 10 ml after 1 and after 3 days) was stirred under N_2 and under reflux for 5 days. The reaction was followed by tlc (on SiO_2, with 5% MeOH in $CHCl_3$). The mixture was filtered and evaporated *in vacuo*. $PhCH_3$ was added and evaporated to remove excess isocyanate, and the resulting gum was crystallized from 250 ml of *i*-PrOH. Thus 18.8 g (88.6%) of white fluffy needles was obtained, mp 103–105°.

Crotyl Isocyanate. To a suspension of 41.54 g (0.256 mole) of 1,1'-carbonyldiimidazole in 100 ml of CH_2Cl_2 was slowly added, with stirring during 0.5 hr at 25°, 18.0 g (0.256 mole) of crotylamine. After standing overnight, the solution was slowly distilled through an 18-cm, glass-helices-packed, column. After removing the CH_2Cl_2, a fraction boiling at 45–46° (56 mm) was collected. This was redistilled at atmospheric pressure yielding 9.7 g (39.9%) of colorless liquid, bp 113°. Ir and nmr support the structure, and gc indicates it was greater than 94.7% pure. Christophersen and Holm[4] report bp 116°.

Cyclopropyl Isocyanate. A suspension of 35.8 g (0.55 mole) of NaN_3 in 200 ml of triethylene glycol dimethyl ether in a 1-l. flask fitted with a stirrer, thermometer, dropping funnel, and a Vigreux column to which was attached a Dry Ice cooled, two-necked flask was cooled to 5°, and 52.25 g (0.5 mole) of cyclopropylcarbonyl chloride was slowly added under N_2 during 10 min. After stirring at 0–25° for 1 hr, the mixture was slowly heated in a water bath. At about 55° N_2 started to come off and it was evolved rapidly at 70–103°. The flask was then heated in an oil bath up to 171°, and the product was distilled at 56 mm. Solvent refluxed in the bottom of the column. The distillate was redistilled through an 18-cm, glass-helices-packed column giving 25.67 g (62%) of colorless liquid, bp 87° (atm), $n^{26}D$ 1.4210; d_4^{25} 1.00. Jones and Scott[5] apparently prepared this but did not isolate or characterize it.

Acknowledgments. The authors wish to thank the following people who contributed to this work: our Physical and Analytical Chemistry Unit for analytical and spectral data; Mr. Bharat V. Kamdar and Mr. Walter Friis for technical assistance.

References

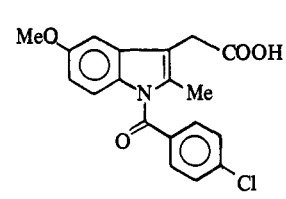
(1) R. B. Moffett and A. D. Rudzik, *J. Med. Chem.*, 14, 588 (1971). (paper 9).
(2) L. H. Sternback, L. O. Randall, R. Banziger, and H. Lehr, "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, New York, N.Y., 1968, Chapter 6, p 252.
(3) Y. Usui, Y. Hara, I. Mikami, and T. Asuda, *Takeda Kenkyusho Nempo*, 30, 145 (1971).
(4) C. Christophersen and A. Holm, *Acta Chem. Scand.*, 24, 1852 (1970).
(5) L. W. Jones and A. W. Scott, *J. Amer. Chem. Soc.*, 44, 407 (1922).
(6) G. H. Youngdale, D. G. Anger, W. C. Anthony, J. P. Da Vanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, 7, 415 (1964).
(7) H. H. Keasling, E. L. Schumann, and W. Veldkamp, *ibid.*, 8, 548 (1965).
(8) J. B. Hester, A. D. Rudzik, and B. V. Kamdar, *ibid.*, 14, 1078 (1971).
(9) J. B. Hester, A. D. Rudzik, H. H. Keasling, and W. Veldkamp, *ibid.*, 13, 23 (1970).

Derivatives of Indole-1-acetic Acid as Antiinflammatory Agents

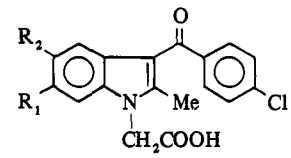
Karl J. Doebel* and Jan W. F. Wasley

Research Department, Pharmaceuticals Division, Ciba-Geigy Corporation, Ardsley, New York 10502. *Received January 7, 1972*

In view of the activity of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (1, Indomethacin) as an antiinflammatory agent, a study of molecular models showed **2** to be spatially similar to Indomethacin (1). The related isomer **3** was sufficiently similar to merit investigation also.



1

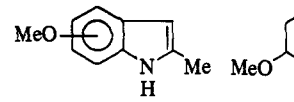


2, R_1 = MeO; R_2 = H
3, R_1 = H; R_2 = MeO

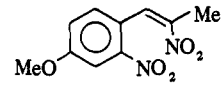
The publication of **2**[1] prompts us to report our findings in this area.

Results and Discussion

Preparation of **2** and **3** proceeded by similar routes, but for **2** the indole **4a** was required. This was prepared by catalytic hydrogenation of **5**.

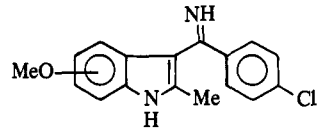


4a, 6-MeO
4b, 5-MeO

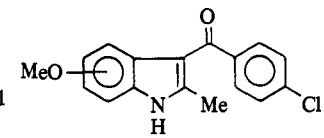


5

The general synthetic pathway involved the condensation of *p*-chlorobenzonitrile with **4a** or **4b** to yield the imines **6a** and **6b**, respectively. It was anticipated that the imines would readily hydrolyze to the corresponding ketones **7a** and **7b**, but this was not the case.



6a, 6-MeO
6b, 5-MeO

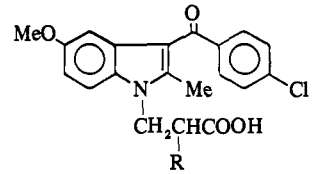


7a, 6-MeO
7b, 5-MeO

Alkylation of **6a** or **6b** with ethyl bromoacetate in acetone in the presence of anhydrous K_2CO_3 proceeded smoothly, and alkaline hydrolysis (3 *N* NaOH) of the intermediate esters gave the desired products **2** and **3**.

A comparison of the pK_{mcs} and distribution coefficients indicated that **2** and **3** are significantly more acidic than Indomethacin (1), as can be seen from Table I.

In order to obtain molecules with acidity similar to indomethacin (1), the corresponding 1-propionic and 1-isobutyric acid derivatives **8** and **9** were prepared by the con-



8, R = H
9, R = Me

densation of **6b** with methyl acrylate and methyl methacrylate, respectively, followed by alkaline hydrolysis of the intermediate esters. As can be seen from Table I, the acidity of these compounds now approximates that of 1.

Table I

Compound	pK_{mcs}	*P* ($CHCl_3$–aqueous buffer, pH 6.9)
1	6.45	37.2
2	4.97	0.13
3	5.00	0.13
8	6.08	11.9
9	6.26	60.0

Biological Activity. Antiinflammatory tests were performed on compounds 2, 3, 8, and 9 using the uv erythema screen[2] (guinea pigs) and anticarrageenin (rat paw edema) screen.[3]

Compounds 2 and 3 were inactive in these screens. Compounds 8 and 9 showed marginal activity in the anticarrageenin screen, 14 and 12%, respectively, at 100 mg/kg po, and 9 exhibited 44% inhibition in the uv erythema test at 100 mg/kg po.

By comparison 1 caused 39 and 48% inhibition in the anticarrageenin screen at doses of 2 and 4 mg/kg po, respectively. In the uv test 1 exhibited 58% inhibition at a dose of 4 mg/kg po.

Experimental Section†

3-Nitro-4-(2-nitropropenyl)anisole (5). This was prepared from 2-nitroanisaldehyde[5] (10 g) and nitroethane (7 ml) by the method of Beer, *et al.*[6] The product crystallized from ethanol as long yellow needles (5.5 g, 38.3%), mp 109–110°.

6-Methoxy-2-methylindole (4a). To 3-nitro-4-(2-nitropropenyl)-anisole (5 g, 0.02 mole) in glacial AcOH (125 ml) and EtOH (125 ml) was added 5% Pd/C (1 g), and the mixt was hydrogenated at atm pressure and room temp until 6 mole equiv of H_2 was absorbed. The catalyst was filtered, and the filtrate neutralized with $NaHCO_3$ in the presence of Et_2O. The neutralized soln was further extracted with Et_2O (3 × 500 ml), dried (Na_2CO_3), and evapd to yield a pale green solid. This was purified by Soxhlet extraction with petr ether (bp 60–80°), yielding colorless prisms (2.5 g, 75%), mp 102–103° (lit.[7] 102–103°).

3-*p*-Chlorobenzimidoyl-6-methoxy-2-methylindole (6a). Crude 6-methoxy-2-methylindole (7.5 g, 0.046 mole) and *p*-chlorobenzonitrile (18.8 g, 0.14 mole) were dissolved in 50 ml of Et_2O. Anhydrous HCl was bubbled through the soln for 8 hr. A solid pptd initially, then redissolved after about 2 hr. After 5 hr, a solid again began to separate. The reaction flask was stoppered and stored at 5° for 5 days. The Et_2O was decanted, fresh Et_2O (100 ml) was added, and the mixt was stirred for 1 hr. The imine HCl was removed by filtration, dried *in vacuo*, dissolved in hot EtOH, and basified (pH 9) with 10% NH_4OH. The product crystd from $CHCl_3$–petr ether as off-white prisms (2.5 g, 17%), mp 204–205°. *Anal.* ($C_{17}H_{15}ClN_2O$) N.

3-*p*-Chlorobenzoyl-6-methoxy-2-methylindole-1-acetic Acid (2). A mixt of 3-*p*-chlorobenzimidoyl-6-methoxy-2-methylindole (5.25 g, 0.017 mole), ethyl bromoacetate (3.3 g, 0.02 mole), reagent grade Me_2CO (30 ml), and anhyd K_2CO_3 (16 g) was heated under reflux for 18 hr. After cooling, the solid was filtered and washed well with Me_2CO (250 ml). The filtrates were evapd yielding a brown oily residue (≃5 g), which was heated under reflux with 3 *N* NaOH (75 ml) for 2 hr. The Na salt of 2 was crystd from the mixt, collected by filtration, and dissolved in hot H_2O (1 l.), and the soln filtered to remove the insol by-product 7a. Acidification of the filtrate with 10% H_2SO_4 yielded a pale yellow ppt which was collected, dried *in vacuo*, and then crystd from EtOH as pale yellow needles (1.5 g, 25%), mp 237–238°. *Anal.* ($C_{19}H_{16}ClNO_4$) C, H, N, Cl.

3-*p*-Chlorobenzimidoyl-5-methoxy-2-methylindole (6b). This was prepared in a manner analogous to 3-*p*-chlorobenzimidoyl-6-methoxy-2-methylindole (6a). The product crystd from aqueous EtOH as colorless needles (43%), mp 190–192°. *Anal.* ($C_{17}H_{15}ClN_2O$) C, H, N, Cl.

3-*p*-Chlorobenzoyl-5-methoxy-2-methylindole-1-acetic Acid (3). This was prepared in a manner analogous to 3-*p*-chlorobenzoyl-6-methoxy-2-methylindole-1-acetic acid (2). The product crystd from EtOH as colorless needles (33%), mp 248–249°. *Anal.* ($C_{19}H_{16}ClNO_4$) C, H, N, Cl.

3-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-1-propionic Acid (8). 3-*p*-Chlorobenzimidoyl-5-methoxy-2-methylindole (5.0 g, 0.017 mole), methyl acrylate (1.7 g, 0.017 mole), Me_2CO (150 ml), and anhyd K_2CO_3 (1.0 g) were combined and heated under reflux for 72 hr. On cooling, the solid was filtered and washed well with Me_2CO (100 ml). The combined filtrates were evapd to yield a brown oily residue, which was heated under reflux with 3 *N* NaOH (50 ml) until a homogenous soln was obtained (~2 hr). On cooling, a white ppt formed (Na salt), which was collected by filtration, dissolved in hot H_2O (750 ml), and acidified (pH 2) with 10% H_2SO_4. The product was collected, dried *in vacuo*, and crystd from EtOH as colorless needles (3.6 g, 58%). *Anal.* ($C_{20}H_{18}ClNO_4$) C, H, N, Cl.

3-(*p*-Chlorobenzoyl)-5-methoxy-α,2-dimethylindole-1-propionic Acid (9). 3-*p*-Chlorobenzimidoyl-5-methoxy-2-methylindole (5.0 g, 0.017 mole) and methyl methacrylate (10 g, 0.1 mole) reacted under conditions similar to those for 8. The product was recrystd from EtOH as pale yellow needles (400 mg, 6.2%), mp 178–179°. *Anal.* ($C_{21}H_{20}ClNO_4$) C, H, N, Cl.

Acknowledgments. We wish to express our appreciation to Mrs. M. L. Graeme and coworkers for the antiinflammatory testing and to Mr. S. Lopoukhine for technical assistance. We are indebted to Mrs. M. Myers and associates for the microanalyses.

References

(1) Roussel-UCLAF, French Patent 5.173M (1966).
(2) C. V. Winder, J. Wax, V. Burr, M. Been, and C. E. Rosiere, *Arch. Int. Pharmacodyn.*, 116, 261 (1958).
(3) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).
(4) W. Simon and E. Heilbronner, *Helv. Chim. Acta*, 40, 210 (1957).
(5) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 2, 22 (1958).
(6) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).
(7) E. Späth and O. Brunner, *Ber.*, 58B, 518 (1925).

†Melting points were determined with a Thomas-Hoover apparatus equipped with a corrected thermometer. Microanalyses were performed by the Analytical Research Department of Geigy Chemical Corp. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values. pK_{mcs} were determined by the method of Simon and Heilbronner.[4] Distribution coefficients were detd spectrophotometrically on aqueous buffer solns of the compds equilibrated with $CHCl_3$.

Some Hypotensive Thiadiazoles†

A. M. Grant, S. V. Krees, A. B. Mauger,* W. J. Rzeszotarski, and F. W. Wolff

Research Foundation of the Washington Hospital Center, Washington, D. C. 20010. *Received February 10, 1972*

In two structurally unrelated series of diuretics it has been observed that removal of the sulfamoyl group results in a loss of diuretic activity and the enhancement of hypotensive activity. Firstly, the diuretic benzothiadiazines[2] led to the development of diazoxide[3] and studies of its analogs.[4,5] Secondly, various hypotensive phthalimidines[6,7] related to chlorthalidone[8] were described. We now report a third series structurally unrelated to the other two, derived from acetazolamide.[9] The compounds discussed here, except for some analogous thiazoles, are all related to 2-amino-1,3,4-thiadiazole by substitution in the amino group and, in a few cases, in the 5 position. Derivatives of acetazolamide, a powerful carbonic anhydrase inhibitor, have not previously been described as having hypotensive properties. However, it was observed by Rubin, *et al.*,[10] that "removal of the sulfamoyl group from substances having diuretic properties usually yields compounds lacking diuretic effect but showing antihypertensive activity."

†This project was performed in the George Hyman Memorial Research Building at the Washington Hospital Center and was supported by the Research Foundation of the Washington Hospital Center and by N.I.H. Grant 5RO1 HE12963. A preliminary report of part of this work was given at the National Meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 1970.[1]