

Antiinflammatory Agents. 3.¹ Synthesis and Pharmacological Evaluation of 2-Amino-3-benzoylphenylacetic Acid and Analogues

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A series of substituted derivatives of 2-amino-3-benzoylphenylacetic acid (amfenac) has been synthesized and evaluated for antiinflammatory, analgesic, and cyclooxygenase inhibiting activity. Several derivatives including 157 (4'-chloro), 158 (4'-bromo), and 182 (5-chloro, 4'-bromo) were more potent than indomethacin in these assays.

Initial investigations² into the pharmacological activity of derivatives of 2-amino-3-benzoylphenylacetic acid (1, amfenac, Scheme I), a potent analgesic and nonsteroidal antiinflammatory drug,³ suggested that the potency of 1 could be increased by the addition of certain substituents to the molecule. This article describes the results obtained from a comprehensive structure-activity study of analogues of 1.

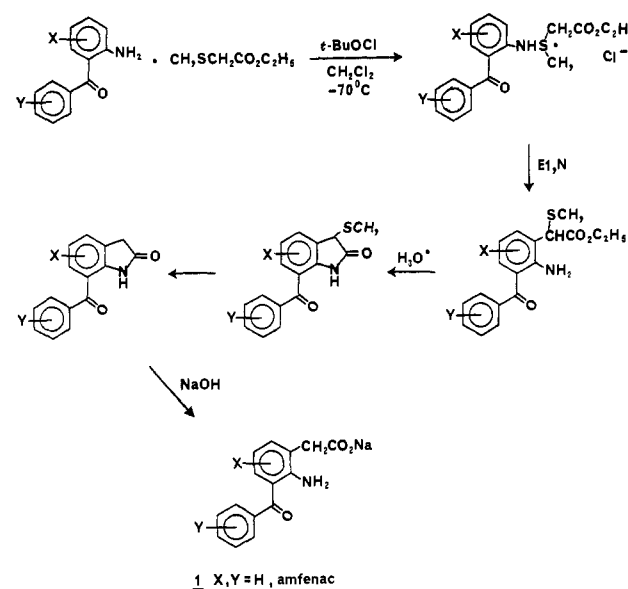
Chemistry. Substituted 7-benzoyloxindoles, precursors to the desired 2-amino-3-benzoylphenylacetic acids, were prepared by two general methods (Schemes I and IV). Gassman's⁴ method for the synthesis of oxindoles, utilizing substituted 2-aminobenzophenones (Table I) as starting material, gave the 3-(methylthio)oxindoles in good yields (Tables II, III) in a one-pot synthetic sequence. Removal of the 3-methylthio group with either Raney nickel or tin and hydrochloric acid gave the oxindoles (Scheme I). In cases where the electron-donating 5-methoxy substituent was required, a modification⁶ of Gassman's original procedure was used due to the instability of the *N*-chloro-*p*-anisidine intermediate.

The reaction of 3-aminobenzophenone under the standard reaction conditions gave exclusively 4-benzoyl-3-(methylthio)oxindole (13) and none of the 6-benzoyl isomer (17). Strongly electron withdrawing groups direct attack to the more hindered ortho position.⁷ The synthesis of 17 is described in Scheme II.

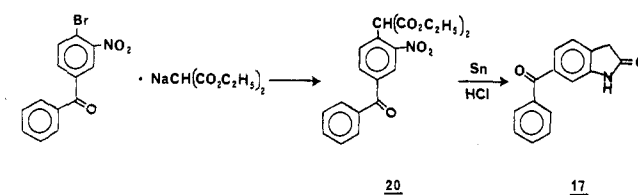
Scheme III depicts some miscellaneous synthetic reactions that gave specific 7-benzoyloxindole derivatives. The 4'-fluoro group of 48 could be displaced with sodium methoxide to give 35 or with sodium thiomethoxide to give 36. The sulfoxide 37 and the sulfone 38 were prepared from 36 by using *m*-chloroperbenzoic acid. The oxindole 54 could be nitrated in concentrated sulfuric acid with potassium nitrate to yield 106. The nitro group was reduced with iron and acetic acid to give the amine 107.

Derivatives containing bromine or iodine were sometimes difficult to prepare by the method outlined in Scheme I since these groups could be partially removed by the Raney nickel or the tin and hydrochloric acid that was used to remove the 3-methylthio group. These halo-

Scheme I



Scheme II



genated derivatives were conveniently prepared by a procedure described by Lo et al.⁸ (Scheme IV). Thus,

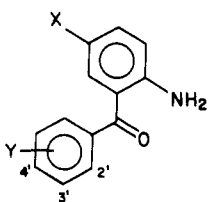
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- (1) For part 2 in this series, see: Walsh, D. A.; Shamblee, D. A.; Welstead, W. J., Jr.; Sancilio, L. F. *J. Med. Chem.* 1982, 25, 446-51.
- (2) Welstead, W. J., Jr.; Moran, H. W.; Taylor, C. R., Jr.; Stauffer, H. F., Jr. "Abstracts of Papers", 170th National Meeting of the American Chemical Society, Chicago, IL, Aug 1975; American Chemical Society: Washington, DC, 1975; MEDI 16.
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- (4) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* 1974, 96, 5508-17.
- (5) Walsh, D. A. *Synthesis* 1980, 677-88.

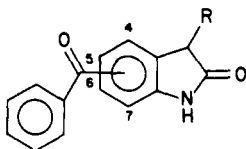
Table I. 2-Aminobenzophenones



| no. | X | Y | mp, °C (solva) | method of prep ^b | % yield | formula |
|-----|------------------|----------------------------------|----------------|-----------------------------|---------|--|
| 2 | H | 3',4'-Cl ₂ | 87-88 (w) | 6.4 | 5 | C ₁₃ H ₉ Cl ₂ NO |
| 3 | H | 4'-C ₆ H ₅ | 142-144 (z) | 6.2 | 27 | C ₁₉ H ₁₅ NO |
| 4 | OCH ₃ | 4'-Cl | 73-75.5 (x) | 6.2 | 67 | C ₁₄ H ₁₂ ClNO ₂ |
| 5 | OCH ₃ | 4'-Br | 68.5-70 (w) | 6.2 | 85 | C ₁₄ H ₁₂ BrNO ₂ |
| 6 | CH ₃ | 4'-F | 70-71.5 (w) | 7.1 | 62 | C ₁₄ H ₁₂ FNO |
| 7 | CH ₃ | 4'-Br | 105.5-107 (w) | 7.1 | 13 | C ₁₄ H ₁₂ BrNO |
| 8 | CH ₃ | 2',4'-Cl ₂ | 69-71 (x) | 7.1 | 78 | C ₁₄ H ₁₁ Cl ₂ NO |
| 9 | F | 4'-CH ₃ | 113-114.5 (w) | 7.1 | 29 | C ₁₄ H ₁₂ FNO |
| 10 | F | 4'-Br | 96-97.5 (w) | 7.1 | 39 | C ₁₃ H ₉ BrFNO |
| 11 | F | 2',4'-Cl ₂ | 60-62.5 (w) | 7.1 | 42 | C ₁₃ H ₈ Cl ₂ FNO |
| 12 | Cl | 4'-Br | 126-127.5 (y) | 6.2 | 18 | C ₁₃ H ₉ BrClNO |

^a w = cyclohexane, x = ligroin, y = 2-propanol, z = 95% ethanol. ^b Numbers refer to sections in ref 5 in which methods of preparation are described.

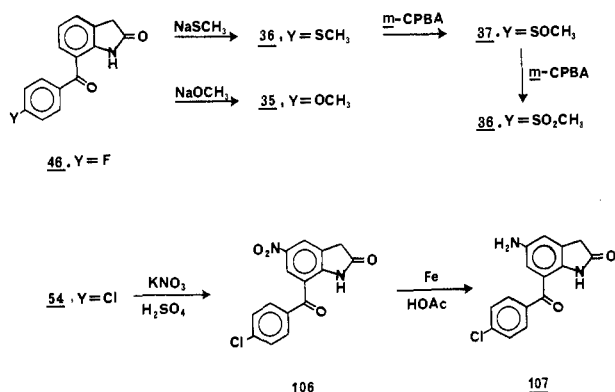
Table II. Benzoyloxindoles



| no. | isomer | R | mp, °C (solva) | method of prep ^b | % yield | formula |
|-----|--------|------------------|----------------|-----------------------------|---------|---|
| 13 | 4 | SCH ₃ | 235-237 (p) | A | 62 | C ₁₆ H ₁₃ NO ₂ S |
| 14 | 4 | H | 210.5-216 (p) | C | 76 | C ₁₅ H ₁₁ NO ₂ |
| 15 | 5 | SCH ₃ | 181-183 (q) | A | 64 | C ₁₆ H ₁₃ NO ₂ S |
| 16 | 5 | H | 204-205 (p) | C | 73 | C ₁₅ H ₁₁ NO ₂ |
| 17 | 6 | H | 209-211 (w) | F | 80 | C ₁₅ H ₁₁ NO ₂ |
| 18 | 7 | SCH ₃ | 130 (x) | A | 80 | C ₁₆ H ₁₃ NO ₂ S |
| 19 | 7 | H | 154 (y) | C | 94 | C ₁₅ H ₁₁ NO ₂ |

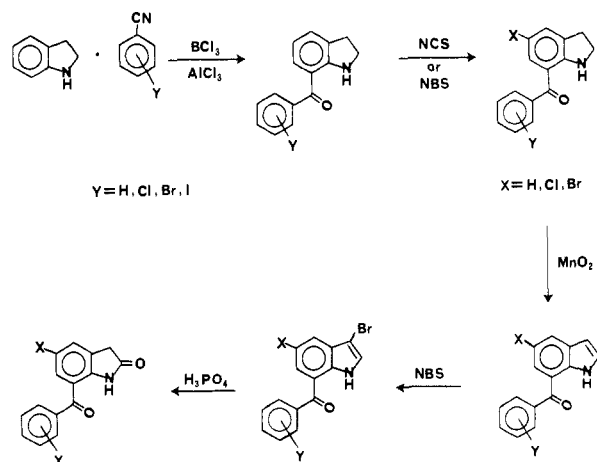
^a p = methanol, q = 2-propanol, w = nitromethane, x = toluene, y = ethanol. ^b Letters refer to methods of preparation described in the Experimental Section.

Scheme III



indoline was benzoylated exclusively in the 7-position under Friedel-Crafts conditions by a modification of the method of Sugawara et al.⁹ The 7-benzoylindoline de-

Scheme IV



ivative was halogenated in the 5-position with either *N*-bromosuccinimide or *N*-chlorosuccinimide (Table IV). Liquid bromine was also used to introduce a bromine in the 5-position. Oxidation with activated manganese dioxide gave the substituted indole. Indoles with no halogen in the 5-position were halogenated in the 3-position with

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(7) Gassman, P. G.; Cue, B. W., Jr.; Luh, T. Y. "Abstracts of Papers", 169th National Meeting of the American Chemical Society, Philadelphia, PA, April 1975; American Chemical Society: Washington, DC, 1975; ORGN 54.

(8) Lo, Y. S.; Walsh, D. A.; Welstead, W. J., Jr.; Mays R. P.; Rose, E. K.; Causey, D. H.; Duncan, R. L. *J. Heterocycl. Chem.* 1980, 17, 1663-4.

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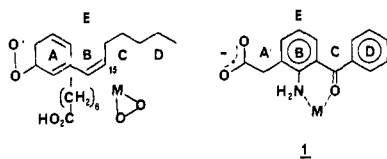


Figure 1.

either *N*-bromosuccinimide or *N*-chlorosuccinimide; however, indoles bearing a halogen in the 5-position would only undergo reaction with *N*-bromosuccinimide (Table V). The 3-haloindoles were hydrolyzed to oxindoles with phosphoric acid in either 2-methoxyethanol or acetic acid.

The substituted oxindoles were hydrolyzed to the aminobenzoylphenylacetic acid sodium salts (Tables VI and VII) most conveniently with 3 N sodium hydroxide at reflux overnight (Scheme I). In one instance, the 4'-fluoro group of **97** was converted to a phenolic hydroxyl (**184**) under the reaction conditions.

Oxindoles **37** (4'-SOCH₃), **38** (4'-SO₂CH₃), **106** (5-NO₂), and **107** (5-NH₂) decomposed under basic hydrolysis conditions.

Results and Discussion

Table VI lists the acute antiinflammatory activity for **1** and several positional isomers. Only **1** possesses activity at 4.0 mg/kg, a dose at which indomethacin is also active. In recent years, there have been various models proposed that describe the binding of a nonsteroidal antiinflammatory drug (NSAID) to the cyclooxygenase enzyme. Many of these models have been reviewed by Bekemeier et al.¹⁰ and they agree with the view¹¹ that the inhibition of prostaglandin formation by NSAIDs is due to their interaction with cyclooxygenase and is responsible for their therapeutic utility. One such model was described by Appleton and Brown¹² and is illustrated in Figure 1. These investigators concluded that the carboxyl group of a NSAID competes with the peroxy group of the precursor peroxy radical of the cyclic endoperoxide (PGG₂) for the same site. In addition, substituents that could occupy a position that is equivalent to carbon atom 15 of the peroxy radical and could chelate to the oxygen-orienting site on the enzyme would be favorable to binding. The fit of **1** in this receptor is excellent. Isomers **138**, **139**, and **140** do not have the benzoyl group ortho to the amino group and the possibility of a bidentate chelation with a metal is lost. Isomer **141**,¹³ while possessing the ortho arrangement of the benzoyl and amino groups, does not have the amino group in a favorable position for chelation.

Derivatives of **1** were tested for their acute antiinflammatory activity and for their ability to inhibit cyclooxygenase obtained from bovine seminal vesicles (Table VII). Addition of a substituent to the ring of **1** containing the amino group (**142** to **148**) decreased antiinflammatory potency with the 5-Cl (**148**) group being the least detrimental. Taylor and Salata¹⁴ have reported that for the tolmetin (1-methyl-5-*p*-toluoylpyrrole-2-acetic acid) series, substitution of a methyl group ortho to the benzoyl substituent increases the inhibition of prostaglandin E₂ syn-

thesis. However, in this series **143** was devoid of antiinflammatory activity of 100 mg/kg in vivo and did not inhibit cyclooxygenase at 1 mM.

Substitution of a group in the benzoyl ring (**149**–**164**) of **1** had a pronounced effect on both the in vitro and in vivo potency. In general, the most potent compounds contained a halogen in the 4'-position with I ~ Br > Cl ~ 2',4'-Cl₂ ~ 2'-Cl, 4'-Br > F ~ SCH₃ > H > CH₃ ~ CF₃ > OCH₃ ~ C₆H₅. Derivatives containing a substituent in the 3'-position (**156** and **163**) were less active than **1** in both test systems.

Compounds that were equipotent to **1** in the acute antiinflammatory test system were then screened in a battery of test systems to determine antiinflammatory activity in a chronic model, analgesic activity, and gastrointestinal irritation liability. Table VIII lists the potency of compounds in relation to that of indomethacin, which has been assigned a potency of 1. Analgesic activity in the acetylcholine-induced abdominal constriction model in mice was determined twice for each compound: once at a pretreatment time of 20 min that gave an indication of onset of action and once at a 5-h pretreatment time that gave an indication of duration of action.

Several compounds listed in Table VIII were very potent antiinflammatory and analgesic agents. It is interesting to note that compounds containing a metabolically labile group such as methyl (**170**, **171**, and **180**) and methylthio (**173** and **179**) were relatively less potent in the chronic model of inflammation and in the analgesia model (5-h pretreatment), suggesting that these compounds were rapidly degraded. Compound **173** was the most potent cyclooxygenase-inhibiting compound tested (Table VII), but its relative potency in the antiinflammatory assay was not retained in vivo.

Compounds that contain a halogen substituent in each ring of **1** are among the most potent prostaglandin synthetase inhibiting compounds reported to date and are very potent in both pharmacological models of inflammation. In order to assess the relative gastrointestinal irritation liabilities of these compounds, therapeutic indexes were computed and are listed in Table IX. The acute therapeutic index is defined as the potency (relative to indomethacin) in the pleural effusion assay/potency (relative to indomethacin) in the gastric toxicity assay, and the chronic therapeutic index is defined as the potency (relative to indomethacin) in the adjuvant-induced arthritis assay/potency (relative to indomethacin) in the intestinal toxicity assay. Several compounds have therapeutic indexes greater than that of indomethacin. As a result, compounds **157**, **158**, and **182** are being developed as analgesic and antiinflammatory agents.

Experimental Section

Pharmacology. A. Antiinflammation. 1. Acute antiinflammatory activity was determined in the Evans blue-carrageenan-induced pleural effusion model by a modification of the method of Sancilio and Fishman.¹⁵ Each compound was administered orally at doses of 100 and 4.0 mg/kg to six fasted rats, and the 5-h effusive response to the intrapleural injection of 5 mL of 0.075% Evans blue–0.5% carrageenan type 7 at 37 °C was measured. Indomethacin at 4.0 mg/kg orally was used for comparison. The data were reported as a percentage decrease in the average volume of pleural fluid from that of the control group. Compounds that were approximately equipotent to **1** were further tested in a battery of pharmacological test systems to determine antiinflammatory potency, analgesic potency, and relative gastrointestinal irritation liability compared with indomethacin

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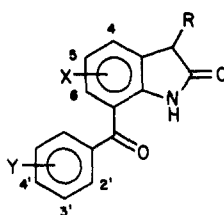
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Table III. Substituted 7-Benzoyloxindoles



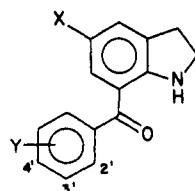
| no. | X | Y | R | mp, °C (solvent) | method of prep ^b | % yield | formula |
|-----|--------------------|---------------------------------------|------------------|------------------|-----------------------------|---------|---|
| 21 | 5-OCH ₃ | H | SCH ₃ | 138-142 (kl) | B | 19 | C ₁₇ H ₁₅ NO ₃ S |
| 22 | 5-OCH ₃ | H | H | 149-152 (m) | C | 29 | C ₁₆ H ₁₃ NO ₃ |
| 23 | 4-CH ₃ | H | SCH ₃ | 122-124 (n) | A | 85 | C ₁₇ H ₁₅ NO ₂ S |
| 24 | 4-CH ₃ | H | H | 177-180 (n) | C | 96 | C ₁₆ H ₁₃ NO ₂ |
| 25 | 5-CH ₃ | H | SCH ₃ | 185-187 (o) | A | 74 | C ₁₇ H ₁₅ NO ₂ S |
| 26 | 5-CH ₃ | H | H | 152-153.5 (n) | C | 84 | C ₁₆ H ₁₃ NO ₂ |
| 27 | 6-CH ₃ | H | SCH ₃ | 162-164 (n) | A | 80 | C ₁₇ H ₁₅ NO ₂ S |
| 28 | 6-CH ₃ | H | H | 176-177 (n) | C | 95 | C ₁₆ H ₁₃ NO ₂ |
| 29 | 5-F | H | SCH ₃ | 157-158 (l) | A | 66 | C ₁₆ H ₁₂ FNO ₂ S |
| 30 | 5-F | H | H | 159.5-166.5 (l) | C | 82 | C ₁₅ H ₁₀ FNO ₂ |
| 31 | 5-Cl | H | SCH ₃ | 213-214 (p) | A | 47 | C ₁₆ H ₁₂ ClNO ₂ S |
| 32 | 5-Cl | H | H | 184-185 (lq) | D | 25 | C ₁₅ H ₁₀ ClNO ₂ |
| 33 | 6-Cl | H | SCH ₃ | 158.5-160.5 (n) | A | 67 | C ₁₆ H ₁₂ ClNO ₂ S |
| 34 | 6-Cl | H | H | 206-209 (n) | C | 80 | C ₁₅ H ₁₀ ClNO ₂ |
| 35 | H | 4'-OCH ₃ | H | 146-147 (l) | G | 51 | C ₁₆ H ₁₃ NO ₃ |
| 36 | H | 4'-SCH ₃ | H | 167-169 (r) | H | 70 | C ₁₆ H ₁₃ NO ₂ S |
| 37 | H | 4'-SOCH ₃ | H | 199-201 (n) | I | 92 | C ₁₆ H ₁₃ NO ₂ S |
| 38 | H | 4'-SO ₂ CH ₃ | H | 254-258 (l) | J | 89 | C ₁₆ H ₁₃ NO ₂ S |
| 39 | H | 4'-CF ₃ | SCH ₃ | 194-197 (n) | A | 56 | C ₁₇ H ₁₂ F ₃ NO ₂ S |
| 40 | H | 4'-CF ₃ | H | 220-223 (l) | C | 80 | C ₁₆ H ₁₀ F ₃ NO ₂ |
| 41 | H | 2'-CH ₃ | SCH ₃ | 131-132 (n) | A | 61 | C ₁₇ H ₁₅ NO ₂ S |
| 42 | H | 2'-CH ₃ | H | 146-148 (n) | C | 83 | C ₁₆ H ₁₃ NO ₂ |
| 43 | H | 4'-CH ₃ | SCH ₃ | 162-163 (l) | A | 77 | C ₁₇ H ₁₅ NO ₂ S |
| 44 | H | 4'-CH ₃ | H | 171-173 (l) | C | 92 | C ₁₆ H ₁₃ NO ₂ |
| 45 | H | 2'-F | SCH ₃ | 147-148.5 (kl) | A | 55 | C ₁₆ H ₁₂ FNO ₂ S |
| 46 | H | 2'-F | H | 209-210 (l) | D | 60 | C ₁₅ H ₁₀ FNO ₂ |
| 47 | H | 4'-F | SCH ₃ | 165-167 (s) | A | 53 | C ₁₆ H ₁₂ FNO ₂ S |
| 48 | H | 4'-F | H | 185-187 (n) | D | 72 | C ₁₅ H ₁₀ FNO ₂ |
| 49 | H | 2'-Cl | SCH ₃ | 142-144 (l) | A | 55 | C ₁₆ H ₁₂ ClNO ₂ S |
| 50 | H | 2'-Cl | H | 170-172 (l) | D | 79 | C ₁₅ H ₁₀ ClNO ₂ |
| 51 | H | 3'-Cl | SCH ₃ | 177-177.5 (l) | A | 85 | C ₁₆ H ₁₂ ClNO ₂ S |
| 52 | H | 3'-Cl | H | 178-180 (l) | C | 83 | C ₁₅ H ₁₀ ClNO ₂ |
| 53 | H | 4'-Cl | SCH ₃ | 186-188 (q) | A | 33 | C ₁₆ H ₁₂ ClNO ₂ S |
| 54 | H | 4'-Cl | H | 177 (q) | C | 93 | C ₁₅ H ₁₀ ClNO ₂ |
| 55 | H | 4'-Br | SCH ₃ | 202-205 (nt) | A | 58 | C ₁₆ H ₁₂ BrNO ₂ S |
| 56 | H | 4'-Br | H | 196-198 (o) | T | 61 | C ₁₅ H ₁₀ BrNO ₂ |
| 57 | H | 4'-I | H | 213-214 (t) | T | 68 | C ₁₅ H ₁₀ INO ₂ |
| 58 | H | 4'-C ₆ H ₅ | SCH ₃ | 149-150 (nr) | A | 66 | C ₂₂ H ₁₇ NO ₂ S |
| 59 | H | 4'-C ₆ H ₅ | H | 212-215 (nt) | C | 93 | C ₂₁ H ₁₅ NO ₂ |
| 60 | H | 2',4'-(CH ₃) ₂ | SCH ₃ | 149-150.5 (n) | A | 75 | C ₁₆ H ₁₇ NO ₂ S |
| 61 | H | 2',4'-(CH ₃) ₂ | H | 176-177.5 (n) | C | 70 | C ₁₇ H ₁₅ NO ₂ |
| 62 | H | 2',4'-Cl ₂ | SCH ₃ | 202-204 (o) | A | 57 | C ₁₆ H ₁₁ Cl ₂ NO ₂ S |
| 63 | H | 2',4'-Cl ₂ | H | 251-256 (nt) | C | 83 | C ₁₅ H ₉ Cl ₂ NO ₂ |
| 64 | H | 3',4'-Cl ₂ | SCH ₃ | 178-181 | A | 48 | C ₁₆ H ₁₁ Cl ₂ NO ₂ S |
| 65 | H | 3',4'-Cl ₂ | H | 191.5-193 (n) | C | 73 | C ₁₅ H ₉ Cl ₂ NO ₂ |
| 66 | H | 2'-Cl, 4'-Br | H | 271-274 (w) | T | 55 | C ₁₅ H ₉ BrClNO ₂ |
| 67 | 5-OCH ₃ | 4'-Cl | SCH ₃ | 142-144.5 (n) | B | 74 | C ₁₇ H ₁₄ ClNO ₃ S |
| 68 | 5-OCH ₃ | 4'-Cl | H | 174.5-176 (n) | C | 90 | C ₁₆ H ₁₂ ClNO ₃ |
| 69 | 5-OCH ₃ | 4'-Br | SCH ₃ | 158.5-160 (nr) | B | 66 | C ₁₇ H ₁₄ BrNO ₃ |
| 70 | 5-OCH ₃ | 4'-Br | H | 180.5-182 (lt) | C | 79 | C ₁₆ H ₁₂ BrNO ₃ |
| 71 | 5-CH ₃ | 4'-SCH ₃ | H | 176-177.5 (kl) | H | 92 | C ₁₇ H ₁₅ NO ₂ S |
| 72 | 5-CH ₃ | 4'-CH ₃ | SCH ₃ | 160-161 (m) | A | 53 | C ₁₈ H ₁₇ NO ₂ |
| 73 | 5-CH ₃ | 4'-CH ₃ | H | 148.5-150 (kl) | C | 83 | C ₁₇ H ₁₅ NO ₂ |
| 74 | 5-CH ₃ | 4'-F | SCH ₃ | 171-172.5 (m) | A | 79 | C ₁₇ H ₁₄ FNO ₂ S |
| 75 | 5-CH ₃ | 4'-F | H | 204-206.5 (kl) | C | 91 | C ₁₆ H ₁₂ FNO ₂ |
| 76 | 5-CH ₃ | 4'-Cl | SCH ₃ | 182.5-184 (l) | A | 72 | C ₁₇ H ₁₄ ClNO ₂ S |
| 77 | 5-CH ₃ | 4'-Cl | H | 167-171 (kl) | C | 79 | C ₁₆ H ₁₂ ClNO ₂ S |
| 78 | 5-CH ₃ | 4'-Br | SCH ₃ | 187-189 | A | 71 | C ₁₇ H ₁₄ BrNO ₂ S |
| 79 | 5-CH ₃ | 4'-Br | H | 179-181.5 (n) | C | 70 | C ₁₆ H ₁₂ BrNO ₂ S |
| 80 | 5-CH ₃ | 2',4'-Cl ₂ | SCH ₃ | 216-217 (kl) | A | 53 | C ₁₇ H ₁₃ Cl ₂ NO ₂ S |
| 81 | 5-CH ₃ | 2',4'-Cl ₂ | H | 211-213 | C | 85 | C ₁₆ H ₁₁ Cl ₂ NO ₂ |
| 82 | 5-F | 4'-SCH ₃ | H | 178-180 (n) | H | 60 | C ₁₆ H ₁₂ FNO ₂ S |
| 83 | 5-F | 4'-CH ₃ | SCH ₃ | 176-178 (n) | A | 66 | C ₁₇ H ₁₄ FNO ₂ S |
| 84 | 5-F | 4'-CH ₃ | H | 189.5-191.5 (m) | C | 86 | C ₁₆ H ₁₂ FNO ₂ |
| 85 | 5-F | 4'-F | SCH ₃ | 171-172.5 (m) | A | 45 | C ₁₆ H ₁₁ F ₂ NO ₂ S |
| 86 | 5-F | 4'-F | H | 195-196.5 (m) | C | 64 | C ₁₅ H ₉ F ₂ NO ₂ |
| 87 | 5-F | 4'-Cl | SCH ₃ | 177-185 | A | 80 | C ₁₆ H ₁₁ ClFNO ₂ S |

Table III (Continued)

| no. | X | Y | R | mp, °C (solv ^a) | method of prep ^b | % yield | formula |
|-----|-------------------|-----------------------|------------------|-----------------------------|-----------------------------|---------|--|
| 88 | 5-F | 4'-Cl | H | 187-189 (r) | C | 84 | C ₁₅ H ₉ ClFNO ₂ |
| 89 | 5-F | 4'-Br | SCH ₃ | 197-198 (rt) | A | 52 | C ₁₆ H ₁₁ BrFNO ₂ S |
| 90 | 5-F | 4'-Br | H | 196-197 (nt) | C | 60 | C ₁₅ H ₉ BrFNO ₂ S |
| 91 | 5-F | 2',4'-Cl ₂ | SCH ₃ | 198-200 | A | 44 | C ₁₆ H ₁₀ Cl ₂ FNO ₂ S |
| 92 | 5-F | 2',4'-Cl ₂ | H | 207-208 | C | 83 | C ₁₅ H ₈ Cl ₂ FNO ₂ S |
| 93 | 5-Cl | 4'-SCH ₃ | H | 179-181 (m) | H | 68 | C ₁₆ H ₁₂ ClNO ₂ S |
| 94 | 5-Cl | 4'-CH ₃ | SCH ₃ | 187-189 (m) | A | 43 | C ₁₇ H ₁₄ ClNO ₂ S |
| 95 | 5-Cl | 4'-CH ₃ | H | 152-155 (x) | C | 74 | C ₁₆ H ₁₂ ClNO ₂ S |
| 96 | 5-Cl | 4'-F | SCH ₃ | 202-204 (m) | A | 43 | C ₁₆ H ₁₁ ClFNO ₂ S |
| 97 | 5-Cl | 4'-F | H | 222-225 (x) | C | 64 | C ₁₅ H ₉ ClFNO ₂ S |
| 98 | 5-Cl | 4'-Cl | SCH ₃ | 199-202 (ny) | A | 35 | C ₁₆ H ₁₁ Cl ₂ NO ₂ S |
| 99 | 5-Cl | 4'-Cl | H | 196-201 | C | 80 | C ₁₅ H ₉ Cl ₂ NO ₂ S |
| 100 | 5-Cl | 4'-Br | SCH ₃ | 208-211 (m) | A | 46 | C ₁₆ H ₁₁ BrClNO ₂ S |
| 101 | 5-Cl | 4'-Br | H | 213-214 (r) | T | 43 | C ₁₅ H ₉ BrClNO ₂ S |
| 102 | 5-Cl | 4'-I | H | 218-221 (r) | T | 48 | C ₁₅ H ₉ ClINO |
| 103 | 5-Cl | 2'-Cl, 4'-Br | H | 255-258 (ry) | T | 33 | C ₁₅ H ₉ BrCl ₂ NO ₂ S |
| 104 | 5-Br | 4'-Cl | H | 206-209 (r) | T | 35 | C ₁₅ H ₉ BrClNO ₂ S |
| 105 | 5-Br | 4'-Br | H | 206-207 (r) | T | 41 | C ₁₅ H ₉ Br ₂ NO ₂ S |
| 106 | 5-NO ₂ | 4'-Cl | H | 253-259 (mz) | K | 75 | C ₁₅ H ₉ ClNO ₂ O ₄ |
| 107 | 5-NH ₂ | 4'-Cl | H | 236-239 (mt) | L | 32 | C ₁₅ H ₁₁ ClN ₂ O ₂ |

^a k = water, l = ethanol, m = ethyl acetate, n = 2-propanol, o = acetonitrile, p = methylene chloride, q = toluene, r = benzene, s = methanol, t = tetrahydrofuran, w = 2-methoxyethanol, x = acetone, y = pyridine, z = dimethylformamide. ^b Letters refer to methods of preparation described in the Experimental Section.

Table IV. 7-Benzoylindoline Derivatives



| no. | X | Y | mp, °C (solv ^a) | method of prep ^b | % yield | formula |
|-----|----|--------------|-----------------------------|-----------------------------|---------|--|
| 108 | H | 4'-Cl | 107-108 (w) | M | 91 | C ₁₅ H ₁₂ ClNO |
| 109 | H | 4'-Br | 128-129 (x) | M | 76 | C ₁₅ H ₁₂ BrNO |
| 110 | H | 4'-I | 149-150 (y) | M | 85 | C ₁₅ H ₁₂ INO |
| 111 | H | 2'-Cl, 4'-Br | 120-121 (x) | M | 55 | C ₁₅ H ₁₁ BrClNO |
| 112 | Cl | 4'-Cl | 146-148 (y) | N | 45 | C ₁₅ H ₁₁ Cl ₂ NO |
| 113 | Cl | 4'-Br | 168-169 (z) | N | 67 | C ₁₅ H ₁₁ BrClNO |
| 114 | Cl | 4'-I | 175 (z) | N | 54 | C ₁₅ H ₁₁ ClINO |
| 115 | Cl | 2'-Cl, 4'-Br | 113-118 (x) | N | 68 | C ₁₅ H ₁₀ BrCl ₂ NO |
| 116 | Br | 4'-Cl | 157-159 (z) | P | 49 | C ₁₅ H ₁₁ BrClNO |
| 117 | Br | 4'-Br | 167.5-168 (z) | O | 89 | C ₁₅ H ₁₁ Br ₂ NO |

^a w = petroleum ether, x = 2-propanol, y = absolute ethanol, z = ethyl acetate. ^b Letters refer to methods of preparation described in the Experimental Section.

(Table VIII). Potencies relative to indomethacin were determined by regression analysis.

2. Chronic antiinflammatory activity was determined in the adjuvant-induced arthritic rat model of Walz et al.¹⁶ using a therapeutic rather than a prophylactic dosing regimen as described by Sancilio et al.¹⁷

B. Analgesia. Oral analgesic activity was determined in mice by the acetylcholine-induced abdominal constriction assay.¹⁷ Acetylcholine bromide was administered intraperitoneally 20 min or 5 h following oral administration of the test compound. Zompirac was used as a standard.

C. Gastrointestinal Liability. 1. **Acute Gastric Toxicity (Single Oral Dose).** Male fasted rats weighing between 150 and 200 g were randomly divided into groups of seven. The compounds were dissolved or suspended in 0.5% Tween 80 and administered by gavage (10 mL/kg). Six hours later, the animals were killed with chloroform or carbon dioxide. The stomachs were removed, washed, and examined for the presence of erosions. On a blind

basis, the degree of damage was scored according to the following system: 1, one to three erosions <3 mm in diameter; 2, many small erosions; 3, two to three erosions greater than 3 mm in diameter or 4-5 mm in length; and 4, four or more large erosions.

2. **Chronic Intestinal Toxicity (Multiple Oral Doses).** Male and female Sprague-Dawley rats, weighing between 160 and 200 g, were randomly divided into groups of eight. Excluding the weekend, compounds were orally administered on a daily basis for 11 days. Twenty-four hours after the last dose, the rats were killed with chloroform or carbon dioxide and the intestines were examined for the presence of ulcers. The severity of the lesions was scored in increments of 10, from 0 for no damage to +40 for maximum damage, plus 10 for perforations and/or adhesions, and an additional 10 if the animal died. Growth of the animals was also monitored during the course of the experiment.

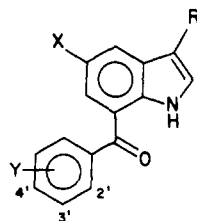
D. Prostaglandin Synthetase Inhibition. The polarographic method used for the determination of the inhibition of cyclooxygenase obtained from bovine seminal vesicles has been described in detail.¹

General Procedures. Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected; ¹H NMR spectra were obtained in CDCl₃ or Me₂SO-*d*₆ with Me₄Si as internal standard or in D₂O with sodium 3-(trimethylsilyl)propionate-*d*₄ as internal standard on a Varian

(16) Walz, D. T.; Di Martino, M. J.; Misher, A. J. *Pharmacol. Exp. Ther.* 1971, 178, 223-31.

(17) Sancilio, L. F.; Reese, D. L.; Cheung, S.; Alphin, R. S. *Agents Actions* 1977, 7, 133-44.

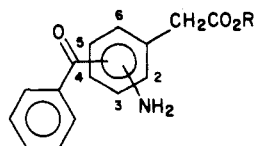
Table V. 7-Benzoylindole Derivatives



| no. | X | Y | R | mp, °C (solva) | method of prep ^b | % yield | formula |
|-----|----|--------------|----|----------------|-----------------------------|---------|--|
| 118 | H | 4'-Cl | H | 149-151 (p) | Q | 69 | C ₁₅ H ₁₀ ClNO |
| 119 | H | 4'-Cl | Cl | 192-193 (p) | R | 45 | C ₁₅ H ₉ Cl ₂ NO |
| 120 | H | 4'-Br | H | 161-163 (p) | Q | 85 | C ₁₅ H ₁₀ BrNO |
| 121 | H | 4'-Br | Cl | 193-194 (p) | R | 64 | C ₁₅ H ₉ BrClNO |
| 122 | H | 4'-I | H | 175-176 (q) | Q | 97 | C ₁₅ H ₁₀ I ₂ NO |
| 123 | H | 4'-I | Cl | 179-180 (q) | R | 81 | C ₁₅ H ₉ ClINO |
| 124 | H | 2'-Cl, 4'-Br | H | 144-146 (w) | Q | 93 | C ₁₅ H ₉ BrClNO |
| 125 | H | 2'-Cl, 4'-Br | Cl | 155-157 (w) | R | 98 | C ₁₅ H ₈ BrCl ₂ NO |
| 126 | Cl | 4'-Cl | H | 170-171 (w) | Q | 89 | C ₁₅ H ₉ Cl ₂ NO |
| 127 | Cl | 4'-Cl | Br | 220-221 (p) | S | 58 | C ₁₅ H ₈ BrCl ₂ NO |
| 128 | Cl | 4'-Br | H | 183.5-185 (p) | Q | 98 | C ₁₅ H ₉ BrClNO |
| 129 | Cl | 4'-Br | Br | 224-226 (q) | S | 85 | C ₁₅ H ₈ Br ₂ ClNO |
| 130 | Cl | 4'-I | H | 171-173 (x) | Q | 92 | C ₁₅ H ₉ ClINO |
| 131 | Cl | 4'-I | Br | 223-224 (q) | S | 84 | C ₁₅ H ₈ BrClINO |
| 132 | Cl | 2'-Cl, 4'-Br | H | 184-185 (x) | Q | 99 | C ₁₅ H ₉ BrCl ₂ NO |
| 133 | Cl | 2'-Cl, 4'-Br | Br | 162-162.5 (x) | S | 99 | C ₁₅ H ₁₇ Br ₂ Cl ₂ NO |
| 134 | Br | 4'-Cl | H | 183-184 (qy) | Q | 79 | C ₁₅ H ₉ BrClNO |
| 135 | Br | 4'-Cl | Br | 215-217 (p) | S | 97 | C ₁₅ H ₈ Br ₂ ClNO |
| 136 | Br | 4'-Br | H | 201-202.5 (p) | Q | 100 | C ₁₅ H ₉ Br ₂ NO |
| 137 | Br | 4'-Br | Br | 226-228 (pz) | S | 81 | C ₁₅ H ₁₈ Br ₃ NO |

^ap = ethyl acetate, q = benzene, w = 2-propanol, x = absolute ethanol, y = cyclohexane, z = tetrahydrofuran. ^bLetters refer to methods of preparation described in the Experimental Section.

Table VI. Oral Antiinflammatory Activity in the 5-h Evans Blue-Carrageenan Pleural Effusion Assay for Aminobenzoylphenylacetic Acids



| no. | NH ₂ | PhC(=O) | R | mp, °C (solva) | % yield | formula | % change in av vol of pleural fluid, dose (mg/kg) | |
|------------------|-----------------|---------|----|----------------|---------|---|---|-------------------------|
| | | | | | | | compd (4.0) | indo ^b (4.0) |
| 1 | 2 | 3 | Na | 248-252 (wx) | 80 | C ₁₅ H ₁₂ NNaO ₃ ·H ₂ O | -26 | -33 |
| 138 | 2 | 4 | Na | 244-245 (x) | 65 | C ₁₅ H ₁₂ NNaO ₃ ·0.5H ₂ O ^c | -2 ^d | -31 |
| 139 | 2 | 5 | H | 150-151 (wx) | 85 | C ₁₅ H ₁₃ NO ₃ | 11 ^d | -43 |
| 140 | 2 | 6 | Na | 254.5-256 (wy) | 51 | C ₁₆ H ₁₂ NNaO ₃ ·H ₂ O | -2 ^d | -35 |
| 141 ^e | 4 | 3 | H | 133-134 (z) | 52 | C ₁₅ H ₁₃ NO ₃ | -4 ^d | -31 |

^aw = water, x = ethanol, y = 2-propanol, z = benzene. ^bIndomethacin. ^cC: calcd, 62.94; found, 62.45. ^dNot significantly different from control group at $p < 0.05$, as determined by the Dunnett's t test. ^eReference 16.

A-60, a Varian EM-360L, or a Varian FT-80A spectrometer; mass spectra were determined on a Varian MAT-44 or on a Hitachi Perkin-Elmer RMU-6H mass spectrometer; IR spectra were run as KBr pellets on a Beckman IR8 or on a Perkin-Elmer 297 IR spectrophotometer; analytical results for compounds followed by elemental symbols are within $\pm 0.4\%$ of theory and were determined on a Perkin-Elmer Model 240 CHN analyzer. Spectral data for all reported compounds were consistent with assigned structures. Indomethacin was obtained from Merck and Co., Inc. and zompirac was obtained from McNeil Pharmaceutical.

Method A. 7-(2-Chlorobenzoyl)-1,3-dihydro-3-(methylthio)-2H-indol-2-one (49). A solution of 50 g (0.216 mol) of 2'-chloro-2-aminobenzophenone^b in 800 mL of methylene chloride was cooled to -70°C and 30.5 g (0.227 mol) of ethyl (methylthio)acetate was added. The cold mixture was stirred vigorously while 26.0 g (0.227 mol) of 95% *tert*-butyl hypochlorite (Frinton Labs) was added dropwise. The mixture was stirred at -70°C for 1 h and then 25 g (0.25 mol) of triethylamine was added. The

mixture was allowed to warm to ambient temperature and 400 mL of 3 N hydrochloric acid was added. The mixture was heated at reflux with vigorous stirring for 2 h. The organic phase was separated and concentrated and the residue was recrystallized from 95% ethanol to give 38.0 g (55%) of 49 as pale yellow needles, mp 142-144 $^\circ\text{C}$. Anal. (C₁₅H₁₂ClNO₂S) C, H, N.

Method B. 7-(4-Chlorobenzoyl)-1,3-dihydro-5-methoxy-3-(methylthio)-2H-indol-2-one (67). To a solution of 4.0 mL (0.088 mol) of chlorine in 200 mL of methylene chloride (CH₂Cl₂) cooled to -70°C was added dropwise a solution of 11.8 g (0.088 mol) of ethyl (methylthio)acetate in 30 mL of CH₂Cl₂, while the temperature was maintained below -65°C . After 5 min, a solution of 53 g (0.2 mol) of 4 in 100 mL of CH₂Cl₂ was added dropwise over a 30-min period. The mixture was stirred at -70°C for 1.5 h and 18 g (0.18 mol) of triethylamine was added. The mixture was stirred for 1 h at -70°C and then allowed to warm to ambient temperature. The mixture was treated with 30 mL of concentrated hydrochloric acid and stirred for 1 h. The mixture was filtered

Table VII. Oral Antiinflammatory Activity in the 5-h Evans Blue-Carrageenan Pleural Effusion Assay and Cyclooxygenase Inhibition Data for Substituted 2-Amino-3-benzoylphenylacetic Acids

| no. | X | Y | mp, °C (solv ^a) | % yield | formula ^b | % change in av vol of pleural fluid | | | | cyclooxygenase inhib: IC ₅₀ , μM |
|--------------|--------------------|---------------------------------------|-----------------------------|---------|--|-------------------------------------|------------------|-----------------------------------|------------------|---|
| | | | | | | dose, mg/kg | | indo ^c dose, 4.0 mg/kg | | |
| 1 | H | H | 248-252 (pq) | 80 | C ₁₅ N ₁₂ NNaO ₃ ·H ₂ O | -35 | -26 | -13 ^d | -33 | 0.2 |
| 142 | 5-OCH ₃ | H | 265 | 80 | C ₁₆ H ₁₄ NNaO ₄ ·1.5H ₂ O | | -18 | | -48 ^e | 5.4 |
| 143 | 4-CH ₃ | H | 206-207 (w) | 86 | C ₁₆ H ₁₄ NNaO ₃ ·0.25H ₂ O | -13 ^d | -1 ^d | | -38 | >1000 |
| 144 | 5-CH ₃ | H | 252 (w) | 58 | C ₁₆ H ₁₄ NNaO ₃ ·0.5H ₂ O | -35 | -11 ^d | | -25 | 11 |
| 145 | 6-CH ₃ | H | 235-238 (w) | 69 | C ₁₆ H ₁₄ NNaO ₃ ·0.25H ₂ O | -39 | 2 ^d | | -38 | 3 |
| 146 | 5-F | H | 253 (pq) | 41 | C ₁₆ H ₁₁ FNNaO ₃ ·0.5H ₂ O | -33 | -9 ^d | | -20 | 0.2 |
| 147 | 4-Cl | H | 229-231 (pq) | 57 | C ₁₆ H ₁₁ ClNNaO ₃ ·0.25H ₂ O | -45 | -4 ^d | | -35 | 37 |
| 148 | 5-Cl | H | 260 (qw) | 82 | C ₁₆ H ₁₁ ClNNaO ₃ | | -17 | | -35 | 1 |
| 149 | H | 4'-OCH ₃ | 230-232 (q) | 29 | C ₁₆ H ₁₄ NNaO ₄ ·0.5H ₂ O | | -10 ^d | | -35 | 68 |
| 150 | H | 4'-SCH ₃ | 244-247 (pq) | 83 | C ₁₆ H ₁₄ NNaO ₃ S·H ₂ O | | -21 | | -30 | 0.1 |
| 151 | H | 4'-CF ₃ | 265 (qw) | 65 | C ₁₆ H ₁₁ F ₃ NNaO ₃ ·0.5H ₂ O | | -24 | | -38 | 1 |
| 152 | H | 2'-CH ₃ | 268-272 (w) | 71 | C ₁₆ H ₁₄ NNaO ₃ ·0.25H ₂ O | -32 | -13 ^d | | -25 | 1 |
| 153 | H | 4'-CH ₃ | 264 (pq) | 51 | C ₁₆ H ₁₄ NNaO ₃ | | -17 | | -39 | 0.3 |
| 154 | H | 4'-F | 260 (wx) | 35 | C ₁₆ H ₁₁ FNNaO ₃ | | -36 | 0 ^d | -35 | 0.9 |
| 155 | H | 2'-Cl | 260 | 64 | C ₁₆ H ₁₁ ClNNaO ₃ ·H ₂ O | -42 | -22 | | -33 | 0.3 |
| 156 | H | 3'-Cl | >250 (pq) | 18 | C ₁₆ H ₁₁ ClNNaO ₃ ·0.5H ₂ O | -35 | -15 | | -33 | >1000 |
| 157 | H | 4'-Cl | 265 (p) | 67 | C ₁₆ H ₁₁ ClNNaO ₃ ·0.75H ₂ O | -38 | -29 | -16 | -33 | 0.3 |
| 158 | H | 4'-Br | 285 (pq) | 54 | C ₁₆ H ₁₁ BrNNaO ₃ | | -43 | -27 | -41 | 0.08 |
| 159 | H | 4'-I | 280-282 (wy) | 55 | C ₁₆ H ₁₁ I NNaO ₃ ·0.25H ₂ O | -44 | -31 | -17 | -32 | 0.07 |
| 160 | H | 4'-C ₆ H ₅ | 246-247 (p) | 25 | C ₂₁ H ₁₈ NNaO ₃ ·0.25H ₂ O | -14 ^d | -15 ^d | | -36 | 0.08 |
| 161 | H | 2',4'-(CH ₃) ₂ | 240 | 91 | C ₁₇ H ₁₆ NNaO ₃ | -38 | -3 ^d | | -40 | 0.1 |
| 162 | H | 2',4'-Cl ₂ | 235-240 (px) | 62 | C ₁₆ H ₁₀ Cl ₂ NNaO ₃ ·0.5H ₂ O | -41 | -37 | -16 | -33 | 0.6 |
| 163 | H | 3',4'-Cl ₂ | 260-265 (pqx) | 18 | C ₁₆ H ₁₀ Cl ₂ NNaO ₃ ·1.75H ₂ O | | -10 ^d | | -30 | 50 |
| 164 | H | 2'-Cl, 4'-Br | 125-130 (pw) | 72 | C ₁₆ H ₁₀ BrClNNaO ₃ ·0.5H ₂ O | -37 | -26 | | -32 | 0.05 |
| 165 | 5-OCH ₃ | 4'-Cl | 215-220 (w) | 47 | C ₁₆ H ₁₃ ClNNaO ₄ ·0.25H ₂ O | -36 | -26 | | -37 | 12 |
| 166 | 5-OCH ₃ | 4'-Br | 245-250 (p) | 44 | C ₁₆ H ₁₃ BrNNaO ₄ | -33 | -28 | | -25 | 0.9 |
| 167 | 5-CH ₃ | 4'-CH ₃ | 118-120 | 45 | C ₁₇ H ₁₇ NO ₃ ^f | -33 | -12 ^d | | -42 | 30 |
| 168 | 5-CH ₃ | 4'-SCH ₃ | 225-260 (p) | 37 | C ₁₇ H ₁₆ NNaO ₃ S·2H ₂ O | -47 | -26 | | -42 | 0.4 |
| 169 | 5-CH ₃ | 4'-F | 140-160 (pw) | 17 | C ₁₆ H ₁₃ FNNaO ₃ ·H ₂ O | -35 | 0 ^d | | -42 | 17 |
| 170 | 5-CH ₃ | 4'-Cl | 262 (p) | 18 | C ₁₆ H ₁₃ ClNNaO ₃ | -38 | -32 | 0 ^d | -35 | 0.7 |
| 171 | 5-CH ₃ | 4'-Br | 267-270 (wy) | 41 | C ₁₆ H ₁₃ BrNNaO ₃ | -39 | -31 | | -36 | 0.7 |
| 172 | 5-CH ₃ | 2',4'-Cl ₂ | 185-188 | 65 | C ₁₆ H ₁₂ Cl ₂ NNaO ₃ ·0.5H ₂ O | -43 | -24 | | -45 | 1 |
| 173 | 5-F | 4'-SCH ₃ | 241-244 | 75 | C ₁₆ H ₁₃ FNNaO ₃ S·0.25H ₂ O | | -28 | | -33 | 0.008 |
| 174 | 5-F | 4'-CH ₃ | 239-244 (w) | 32 | C ₁₆ H ₁₃ FNNaO ₃ ·0.25H ₂ O | -49 | -32 | | -36 | 0.07 |
| 175 | 5-F | 4'-F | 244-246 (w) | 35 | C ₁₆ H ₁₀ F ₂ NNaO ₃ | -42 | -42 | | -40 | 0.2 |
| 176 | 5-F | 4'-Cl | 237-240 (pqw) | 48 | C ₁₅ H ₁₀ ClFNNaO ₃ ·0.25H ₂ O | -37 | -37 | -15 ^d | -34 | 0.1 |
| 177 | 5-F | 4'-Br | 244-247 (p) | 70 | C ₁₆ H ₁₀ BrFNNaO ₃ ·H ₂ O | -28 | -28 | | -25 | 0.04 |
| 178 | 5-F | 2',4'-Cl ₂ | 215-217 (w) | 68 | C ₁₆ H ₉ Cl ₂ FNNaO ₃ ·0.5C ₃ H ₅ O ^g | -46 | -41 | | -45 | 0.1 |
| 179 | 5-Cl | 4'-SCH ₃ | 259-260 (w) | 39 | C ₁₆ H ₁₃ ClNNaO ₃ S·0.75H ₂ O | -43 | -43 | | -40 | 0.02 |
| 180 | 5-Cl | 4'-CH ₃ | 259-260 (w) | 23 | C ₁₆ H ₁₃ ClNNaO ₃ ·0.25H ₂ O | -44 | -35 | | -40 | 0.02 |
| 181 | 5-Cl | 4'-Cl | >260 (qw) | 43 | C ₁₆ H ₁₀ Cl ₂ NNaO ₃ ·0.25H ₂ O | | -41 | -18 | -32 | 0.3 |
| 182 | 5-Cl | 4'-Br | 264-266 (p) | 40 | C ₁₆ H ₁₀ BrClNNaO ₃ | -38 | -41 | | -40 | 0.02 |
| 183 | 5-Cl | 4'-I | 275-278 (p) | 36 | C ₁₆ H ₁₀ ClI NNaO ₃ ·0.5H ₂ O | -38 | -35 | | -33 | 0.03 |
| 184 | 5-Cl | 4'-OH | 87-89 | 47 | C ₁₆ H ₁₂ ClNO ₄ ·0.75H ₂ O | -21 | -3 ^d | | -40 | 30 |
| 185 | 5-Cl | 2'-Cl, 4'-Br | 125-130 (w) | 69 | C ₁₆ H ₉ BrCl ₂ NNaO ₃ ·H ₂ O | -37 | -25 | | -36 | 0.05 |
| 186 | 5-Br | 4'-Cl | 270-275 (p) | 58 | C ₁₆ H ₁₀ BrClNNaO ₃ ·0.5H ₂ O | -42 | -26 | | -40 | 0.6 |
| 187 | 5-Br | 4'-Br | 268-269 (p) | 74 | C ₁₅ H ₁₀ Br ₂ NNaO ₃ ·0.5H ₂ O | -34 | -30 | | -33 | 0.8 |
| indomethacin | | | | | | | -33 | -7 ^d | | 1 |

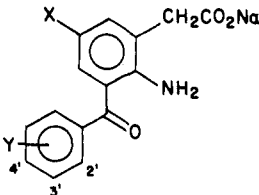
^ap = water, q = absolute ethanol, w = 2-propanol, x = isopropyl ether, y = methanol. ^bAll compounds were analyzed for C, H, and N and results agreed to ±0.4% of theoretical values. ^cIndomethacin. ^dNot significantly different from control group at *p* < 0.05, as determined by the Dunnett's *t* test. ^eAmfenac, 1, used as the reference standard. ^fCharacterized as the acid. ^g0.5 mol of 2-propanol present by NMR.

to remove 4·HCl, and the filtrate was washed with water. The organic solution was concentrated under reduced pressure, and the light brown crystalline residue was recrystallized from 2-propanol to give 22.5 g (74%) of 67 as off-white needles, mp 142.0-144.5 °C. Anal. (C₁₇H₁₄ClNO₃S) C, H, N.

Method C. 7-Benzoyl-6-chloro-1,3-dihydro-2H-indol-2-one (34). A 200-g sample of a commercial (Grace, No. 28) Raney nickel preparation was washed thrice with water, with dilute acetic acid until neutral, and thrice with tetrahydrofuran. The Raney nickel slurry was added cautiously to a solution of 24.7 g (0.078 mol)

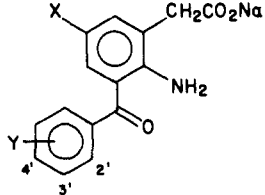
of 33 in 400 mL of tetrahydrofuran and the mixture was mechanically stirred for 10 min. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a solid residue. The solid was recrystallized from 2-propanol to yield 16.9 g (80%) of 34 as a white powder, mp 206-209 °C. Anal. (C₁₅H₁₀ClNO₂) C, H, N.

Method D. 7-(2-Fluorobenzoyl)-1,3-dihydro-2H-indol-2-one (46). A mixture of 60 g (0.2 mol) of 45 and 60 g (0.5 mol) of tin powder in 1 L of 95% ethanol was heated to reflux and 150 mL of concentrated hydrochloric acid was added. Heating was

Table VIII. Pharmacological Potency Relative to Indomethacin of Substituted 2-Amino-3-benzoylphenylacetic Acids


| compd | X | Y | acute | | chronic | | analgesia | |
|-------------------|-------------------|-----------------------|------------------|-------------------|--------------------|---------------------|--------------------------|--------|
| | | | pleural effusion | gastric toxicity | adjuvant arthritis | intestinal toxicity | ED ₅₀ , mg/kg | 20 min |
| indo ^a | | | 1 | 1 | 1 | 1 | 0.22 | 0.22 |
| zom ^b | | | 0.78 | 0.25 | 0.67 | 0.63 | 0.21 | 0.59 |
| 1 | H | H | 0.7 | 0.7 | 1.1 | 0.4 | 0.11 | >3.0 |
| 157 | H | 4'-Cl | 3.8 ^c | 0.9 | 2.2 ^c | 1.4 | 0.10 | 0.93 |
| 158 | H | 4'-Br | 7.5 ^c | 1.4 | 5.8 ^c | 1.8 ^c | 0.07 | 0.13 |
| 159 | H | 4'-I | 6.9 ^c | 5.3 ^c | 8.1 ^c | 3.3 ^c | 0.13 | 0.18 |
| 162 | H | 2',4'-Cl ₂ | 5.3 ^c | 1.0 | 4.2 ^c | 0.6 ^d | 0.21 | >0.3 |
| 164 | H | 2'-Cl, 4'-Br | 1.6 | 5.6 ^c | 7.4 ^c | 1.6 ^c | 0.12 | 1.6 |
| 170 | 5-CH ₃ | 4'-Cl | 1.7 | 0.27 ^c | 0.63 | 0.4 ^d | 0.78 | 0.65 |
| 171 | 5-CH ₃ | 4'-Br | 2.8 ^c | 1.2 | 1.0 | 1.1 | 0.72 | 0.70 |
| 173 | 5-F | 4'-SCH ₃ | 0.4 ^c | e | 0.03 ^c | e | 0.10 | >1.0 |
| 175 | 5-F | 4'-F | 1.4 ^c | 0.37 ^c | 0.01 ^c | e | 0.71 | e |
| 176 | 5-F | 4'-Cl | 3.6 ^c | 1.1 | 1.9 | 0.5 ^c | 0.28 | 1.4 |
| 177 | 5-F | 4'-Br | 8.4 ^c | 1.7 | 2.2 | 1.9 ^d | 0.18 | 0.29 |
| 178 | 5-F | 2',4'-Cl ₂ | 1.2 | 1.0 | 0.13 ^c | e | 0.16 | 0.65 |
| 179 | 5-Cl | 4'-SCH ₃ | 1.8 | 0.9 | 0.1 ^c | e | 0.10 | 1.9 |
| 180 | 5-Cl | 4'-CH ₃ | 1.6 ^d | 0.7 | 0.1 ^c | e | 0.10 | 0.43 |
| 181 | 5-Cl | 4'-Cl | 4.6 ^c | 1.2 | 1.7 | 1.2 | 0.23 | 0.31 |
| 182 | 5-Cl | 4'-Br | 15 ^c | 1.5 ^c | 4.6 ^c | 2.9 ^c | 0.05 | 0.13 |
| 183 | 5-Cl | 4'-I | 3.8 | 3.5 ^c | 5.5 ^c | 2.2 ^c | 0.24 | 0.24 |
| 185 | 5-Cl | 2'-Cl, 4'-Br | 4.9 ^c | 1.2 | 2.5 | 3.3 ^c | 0.66 | 0.19 |
| 187 | 5-Br | 4'-Br | 4.2 ^c | 1.1 | 2.5 | 1.0 | >0.32 | 0.2 |

^a Indomethacin. ^b Zompirac. ^c 95% confidence limits do not overlap 1.0; thus the compound is significantly different than indomethacin. ^d Approximation; regression lines are not parallel. ^e Not tested.

Table IX. Therapeutic Indexes and Biological Data for Selected Substituted 2-Amino-3-benzoylphenylacetic Acids


| compd | X | Y | analgesia | | PG inhib: IC ₅₀ , μM |
|-------------------|------|-------|-----------------------|-------------------------|---------------------------------|
| | | | acute ^a TI | chronic ^b TI | |
| indo ^c | | | 1 | 1 | 0.22 |
| zom ^d | | | 3.1 | 1.1 | 0.59 |
| 1 | H | H | 1 | 2.8 | >3.0 |
| 157 | H | 4'-Cl | 4.3 | 1.6 | 0.93 |
| 158 | H | 4'-Br | 5.4 | 3.2 | 0.13 |
| 159 | H | 4'-I | 1.3 | 2.5 | 0.18 |
| 177 | 5-F | 4'-Br | 4.9 | 1.2 | 0.29 |
| 181 | 5-Cl | 4'-Cl | 3.8 | 1.4 | 0.31 |
| 182 | 5-Cl | 4'-Br | 10 | 1.6 | 0.13 |
| 183 | 5-Cl | 4'-I | 1.1 | 2.5 | 0.24 |

^a Acute therapeutic index = potency in pleural effusion/potency in gastric toxicity assay. ^b Chronic therapeutic index = potency in adjuvant-induced arthritis assay/potency in intestinal toxicity assay. ^c Indomethacin. ^d Zompirac.

continued for 18 h, then the mixture was cooled, and the precipitate was collected by decanting the slurry from the remaining tin and filtering the slurry. The filter cake was recrystallized twice from absolute ethanol to give 31 g (60%) of 46 as white needles, mp 209–210 °C. Anal. (C₁₅H₁₀FNO₂) C, H, N.

Method E. Diethyl 2-(4-Benzoyl-2-nitrophenyl)propane-dioate (20). A mixture of 9.3 g (0.22 mol) of washed (petroleum ether) 57% sodium hydride/oil and 200 mL of dimethyl sulfoxide was heated under a nitrogen atmosphere to 100 °C and treated with a solution of 35.2 g (0.22 mol) of diethyl malonate in 50 mL

of dimethyl sulfoxide. The mixture was stirred for 10 min until a clear solution was present. A solution of 30.6 g (0.1 mol) of 4-bromo-3-nitrobenzophenone¹⁸ in 100 mL of dimethyl sulfoxide was added and the dark reaction mixture was heated at 100 °C for 1 h. The solution was poured into 3 L of water and the mixture was extracted twice with ethyl ether. The combined extracts were washed with water, dried (Na₂SO₄), and concentrated under reduced pressure to give 40 g of an oil, which immediately crystallized. The solid was recrystallized from 2-propanol to yield 35.4 g (92%) of 20 as tan needles, mp 69–71 °C. Anal. (C₂₀H₁₉NO₇) C, H, N.

Method F. 6-Benzoyl-1,3-dihydro-2H-indol-2-one (17). A mixture of 23.1 g (0.06 mol) of 20, 22.4 g (0.19 mol) of tin powder, 150 mL of ethanol, and 65 mL of concentrated hydrochloric acid was heated at reflux for 2 h. The mixture was filtered while hot and a solid crystallized as the filtrate cooled. The solid was collected by filtration and recrystallized from nitromethane to yield 11.4 g (80%) of 17 as tan plates, mp 209–211 °C. Anal. (C₁₅H₁₁NO₂) C, H, N.

Method G. 1,3-Dihydro-7-(4-methoxybenzoyl)-2H-indol-2-one (35). A slurry of 20.5 g (0.08 mol) of 48 in 500 mL of benzene was mixed with a solution of 18.4 g (0.8 mol) of sodium metal in 500 mL of methanol. The mixture was heated at reflux for 18 h and then cooled and filtered. The filtrate was acidified with concentrated hydrochloric acid and concentrated under reduced pressure. The residue was titrated with water and the precipitate was collected by filtration and dried. The solid was purified by column chromatography (400 g of silica gel, 10% ethyl acetate in benzene). Fractions containing the desired product were combined and concentrated to yield 11.0 g (51%) of 35 as a fluffy, white solid, mp 146–147 °C (ethanol). Anal. (C₁₆H₁₃NO₃) C, H, N.

Method H. 1,3-Dihydro-7-[4-(methylthio)benzoyl]-2H-indol-2-one (36). A solution of sodium methyl mercaptide, prepared from 400 mL of 3 N sodium hydroxide and 24 g (0.5 mol) of methyl mercaptan, was mixed with 25.5 g (0.1 mol) of 48

(18) Montagne, P. *J. Chem. Ber.* 1916, 49, 2262–70.

and the mixture was heated at reflux for 1.5 h, then cooled and made acidic (caution: methyl mercaptan evolved rapidly). The precipitate was collected and recrystallized twice from benzene to give 17.8 g (70%) of **36** as yellow crystals, mp 167–169 °C. Anal. (C₁₈H₁₃NO₂S) C, H, N.

Method I. 1,3-Dihydro-7-[4-(methylsulfonyl)benzoyl]-2H-indol-2-one (**37**). A solution of 21.7 g (0.077 mol) of **36** in 400 mL of chloroform was cooled to 0 °C and 13.4 g (0.077 mol) of *m*-chloroperbenzoic acid was added in small portions. The mixture was stirred at 0–5 °C for 1 h and then extracted with a saturated sodium bicarbonate solution. The organic layer was concentrated under reduced pressure to give a tan powder, which was recrystallized from 2-propanol to yield 21.0 g (92%) of **37** as off-white crystals, mp 199–201 °C. Anal. (C₁₆H₁₃NO₃S) C, H, N.

Method J. 1,3-Dihydro-7-[4-(methylsulfonyl)benzoyl]-2H-indol-2-one (**38**). A solution of 3.0 g (0.01 mol) of **37** in 50 mL of chloroform was cooled to 0 °C and 1.8 g (0.01 mol) of *m*-chloroperbenzoic acid was added in one portion. After approximately 5 min a precipitate formed. This was collected by filtration and recrystallized from ethanol to yield 2.8 g (89%) of **38** as a white solid, mp 254–258 °C dec. Anal. (C₁₆H₁₃NO₄S) C, H, N.

Method K. 7-(4-Chlorobenzoyl)-1,3-dihydro-5-nitro-2H-indol-2-one (**106**). A solution of 13.5 g (0.05 mol) of **54** in 100 mL of concentrated sulfuric acid was cooled to –5 °C and 4.0 g (0.04 mol) of potassium nitrate (MCB) was added in 1-g portions at 5-min intervals. The mixture was stirred at 0 °C for 2 h and then poured into a rapidly stirred ice–water mixture. The precipitate was collected by filtration and slurried with boiling ethyl acetate. The slurry was filtered while hot, and the collected precipitate was recrystallized from a mixture of 60 mL of dimethylformamide and 50 mL of ethyl acetate to give 9.5 g (75%) of **106** as tan-yellow crystals, mp 253–259 °C. Anal. (C₁₅H₉ClN₂O₄) C, H, N.

Method L. 5-Amino-7-(4-chlorobenzoyl)-1,3-dihydro-2H-indol-2-one (**107**). A mixture of 6.4 g (0.02 mol) of **106**, 8 g (0.14 mol) of iron powder, and 50 mL of dimethylformamide was heated to 80 °C and a solution of 9 g (0.15 mol) of acetic acid in 30 mL of ethanol was added dropwise over a 10-min period. The mixture was heated at reflux for 1.5 h and then poured into water. The fine precipitate was collected by filtration and dissolved in 500 mL of hot ethyl acetate. The hot solution was washed with water and then concentrated under reduced pressure to 250 mL. The mixture was cooled and the solid was collected by filtration and recrystallized twice from tetrahydrofuran/ethyl acetate to give 1.8 g (32%) of **107** as yellow crystals, mp 236–239 °C dec. Anal. (C₁₅H₁₁ClN₂O₂) C, H, N.

Method M. (4-Bromophenyl)(2,3-dihydro-1H-indol-7-yl)methanone (**109**). A solution of 53.6 g (0.45 mol) of indoline and 100 g (0.55 mol) of 4-bromobenzonitrile in 350 mL of toluene was heated at reflux with use of a Dean–Stark trap to remove any water present. In another flask 58.6 g (0.50 mol) of boron trichloride was dissolved in 350 mL of cold toluene. The cold boron trichloride solution was transferred to a 3-L round-bottomed flask and treated dropwise with the indoline solution at such a rate that the temperature did not exceed 20 °C with ice-bath cooling. Aluminum chloride (66.6 g, 0.5 mol) was added in portions while the temperature was maintained below 20 °C. The mixture was heated at reflux for 20 h, cooled, and cautiously treated with 100 mL of water and 450 mL of 2 N hydrochloric acid. The mixture was vigorously stirred and heated at reflux for 2.5 h and cooled and the solid collected by filtration and washed with benzene. The solid was then vigorously stirred with 750 mL of water while 150 mL of a 25% sodium hydroxide solution was slowly added and the temperature maintained below 20 °C with ice-bath cooling. The mixture was stirred for 3 h and the solid was collected by filtration and washed with water. The solid was then stirred with 2 L of water for 0.5 h, collected by filtration, washed with water, and air-dried to yield 103.5 g (76%) of **109** as golden needles, mp 128–129 °C (2-propanol). Anal. (C₁₅H₁₂BrNO) C, H, N.

Method N. (5-Chloro-2,3-dihydro-1H-indol-7-yl)(4-chlorophenyl)methanone (**112**). A mixture of 7.7 g (0.03 mol) of **108** and 4.7 g (0.035 mol) of *N*-chlorosuccinimide in 200 mL of methylene chloride was stirred at ambient temperature overnight. The reaction mixture was washed once with water and

twice with a 5% sodium bicarbonate solution. The methylene chloride layer was dried (Na₂SO₄) and concentrated to give 8.3 g of brown solid as residue. The solid was purified by column chromatography (200 g of silica gel, 1:1 benzene–ligroin) to yield 3.9 g (45%) of **112** as a fluffy, dark-yellow solid, mp 146–148 °C (ethanol). Anal. (C₁₅H₁₁Cl₂NO) C, H, N.

Method O. (5-Bromo-2,3-dihydro-1H-indol-7-yl)(4-bromophenyl)methanone (**117**). This reaction was carried out exactly as in reaction N. A mixture of 19.8 g (0.066 mol) of **109**, 11.8 g (0.066 mol) of *N*-bromosuccinimide, and 500 mL of methylene chloride gave, after purification by column chromatography (500 g of silica gel, 25% ligroin in benzene), 22.3 g (89%) of **117** as an orange solid, mp 167.5–168 °C (ethyl acetate). Anal. (C₁₅H₁₁Br₂NO) C, H, N.

Method P. (5-Bromo-2,3-dihydro-1H-indol-7-yl)(4-chlorobenzoyl)methanone (**116**). To a solution of 5.1 g (0.02 mol) of **108** in 100 mL of methylene chloride was added dropwise a solution of 3.2 g (0.02 mol) of bromine in 20 mL of methylene chloride. The reaction mixture was stirred for 0.5 h after the addition was completed. The solid that precipitated was collected by filtration and partitioned between methylene chloride and a saturated sodium bicarbonate solution. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to give 4.1 g (61%) of **116** as a yellow powder, mp 157–159 °C (ethyl acetate). Anal. (C₁₅H₁₁BrClNO) C, H, N.

Method Q. (4-Bromophenyl)(5-chloro-1H-indol-7-yl)methanone (**128**). A mixture of 24.3 g (0.072 mol) of **113** and 22 g (0.25 mol) of activated manganese dioxide (Chemetals) in 1 L of methylene chloride was heated at reflux overnight. The mixture was filtered through Celite and the filtrate was concentrated to yield 23.8 g (98%) of **128** as yellow needles, mp 183.5–185 °C (ethyl acetate). Anal. (C₁₅H₉BrClNO) C, H, N.

Method R. (3-Chloro-1H-indol-7-yl)(4-iodophenyl)methanone (**123**). To a stirred solution of 21.4 g (0.062 mol) of **122** in 650 mL of methylene chloride was added portionwise 8.7 g (0.065 mol) of *N*-chlorosuccinimide over a 15-min period. The mixture was stirred at ambient temperature overnight and washed once with water, and the organic layer was concentrated under reduced pressure. The solid residue was triturated with ethyl ether, collected by filtration, washed with water, and air-dried. The solid was recrystallized from benzene to yield 19.0 g (81%) of **123** as fluffy, off-white needles, mp 179–180 °C. Anal. (C₁₅H₉ClINO) C, H, N.

Method S. (3-Bromo-5-chloro-1H-indol-7-yl)(4-bromophenyl)methanone (**129**). To a stirred solution of 21.5 g (0.064 mol) of **128** in 450 mL of methylene chloride was added portionwise 11.8 g (0.066 mol) of *N*-bromosuccinimide over a 15-min period. The mixture was stirred at ambient temperature overnight, cooled in an ice bath, and filtered. The filter cake was washed with water and air-dried to yield 24.2 g (91%) of **129** as a yellow powder, mp 224–226 °C (benzene). Anal. (C₁₅H₈Br₂ClNO) C, H, N.

Method T. 7-(4-Bromobenzoyl)-5-chloro-1,3-dihydro-2H-indol-2-one (**101**). A solution of 24.2 g (0.059 mol) of **129** in 350 mL of hot (100 °C) 2-methoxyethanol was treated with 75 mL of 86% phosphoric acid. The mixture was heated at reflux for 18 h and then filtered while hot to remove a red-purple impurity. The hot filtrate was treated with charcoal and filtered through Celite. The filtrate was poured into 3 L of water and the solid that precipitated was collected by filtration, washed with water, and dried to give 16 g of crude product. The solid was purified by column chromatography (500 g of silica gel, 7.5% ethyl acetate in benzene), and the combined fractions containing **101** were concentrated under reduced pressure. The residue was recrystallized from benzene to yield 8.8 g (43%) of **101** as an off-white solid, mp 213–214 °C. Anal. (C₁₅H₉BrClNO₂) C, H, N.

Method U. 2-Amino-3-benzoyl-4-methylbenzeneacetic Acid Sodium Salt (**143**). A mixture of 8.0 g (0.032 mol) of **28** and 120 mL of 3 N sodium hydroxide was heated at reflux under a nitrogen atmosphere for 18 h and then cooled and diluted to 400 mL. The orange solution was titrated with concentrated hydrochloric acid to pH 8.2 and filtered. The filtrate was concentrated under reduced pressure and the water was removed from the residue by azeotropic distillation with absolute ethanol. The yellow powder was heated with absolute ethanol and filtered. The filtrate was concentrated and the residue was recrystallized from

2-propanol to give 8.9 g (86%) of 143 as a yellow powder, mp 206–207 °C. Anal. (C₁₆H₁₄NNaO₃) C, H, N.

Method V. 2-Amino-5-methyl-3-(4-methylbenzoyl)-benzeneacetic Acid (167). A mixture of 8.0 g (0.03 mol) of 73 and 100 mL of 3 N sodium hydroxide solution was heated at reflux for 5 h. The red solution was cooled and the solid was collected by filtration. The solid was dissolved in water and titrated to pH 8.5 with concentrated hydrochloric acid. The solution was treated with charcoal and filtered, and the filtrate was cooled and acidified to pH 4.5 with glacial acetic acid. The yellow solid was collected, washed with water, and dried overnight at 25 °C and high vacuum to give 3.8 g (45%) of 167 as a yellow powder, mp 118–120 °C dec. Anal. (C₁₇H₁₇NO₃) C, H, N.

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Registry No. 1, 61941-56-8; 1 free acid, 51579-82-9; 2, 91713-52-9; 3, 91713-53-0; 4, 91713-54-1; 5, 91713-55-2; 6, 91713-56-3; 7, 91713-57-4; 8, 91713-58-5; 9, 91713-59-6; 10, 91713-60-9; 11, 91713-61-0; 12, 60773-48-0; 13, 61085-30-1; 14, 61085-34-5; 15, 91713-62-1; 16, 51135-39-8; 17, 91713-63-2; 18, 61085-33-4; 19, 51135-38-7; 20, 91713-64-3; 21, 91713-65-4; 22, 61085-29-8; 23, 91713-66-5; 24, 91713-67-6; 25, 91713-68-7; 26, 91713-69-8; 27, 91713-70-1; 28, 91713-71-2; 29, 91713-72-3; 30, 91713-73-4; 31, 91713-74-5; 32, 61085-27-6; 33, 91713-75-6; 34, 91713-76-7; 35, 91713-77-8; 36, 77534-16-8; 37, 91713-78-9; 38, 91713-79-0; 39, 91713-80-3; 40, 91713-81-4; 41, 91713-82-5; 42, 91713-83-6; 43, 91713-84-7; 44, 91713-85-8; 45, 77534-14-6; 46, 77534-15-7; 47, 61941-49-9; 48, 61941-48-8; 49, 91713-86-9; 50, 91713-87-0; 51, 91713-88-1; 52, 91713-89-2; 53, 61085-31-2; 54, 61112-01-4; 55, 91713-90-5; 56, 91713-91-6; 57, 91713-92-7; 58, 91713-93-8; 59, 91713-94-9; 60, 91713-95-0; 61, 91713-96-1; 62, 91713-97-2; 63, 91713-98-3; 64, 91713-99-4; 65, 91714-00-0; 66, 91714-01-1; 67, 91714-02-2; 68, 91714-03-3; 69, 91714-04-4; 70, 91714-05-5; 71, 91714-06-6; 72, 91714-07-7; 73, 91714-08-8; 74, 91714-09-9; 75, 83388-22-1; 76, 91714-10-2; 77, 91714-11-3; 78, 91714-12-4; 79, 91714-13-5; 80, 91714-14-6; 81, 91714-15-7; 82, 91714-16-8; 83, 91714-17-9; 84, 91714-18-0; 85, 91714-19-1; 86, 91714-20-4; 87, 91714-21-5; 88, 91714-22-6; 89, 91714-23-7; 90,

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