Synthesis and Antiinflammatory Activity of Some 2-Substituted α-Methyl-5-benzimidazoleacetic Acids

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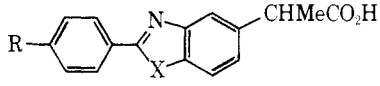
The synthesis of α-methyl-5-benzimidazoleacetic acid (**17**), its 2-amino, 2-phenyl, 2-(4-chlorophenyl), and 2-(4-chlorophenyl)-1-methyl derivatives (**18**, **4**, **3**, and **5**, respectively), and α-methyl-2-oxo-2,3-dihydro-5-benzimidazoleacetic acid (**19**) is described. None of the compounds were effective in reducing carrageenan-induced edema in rat paws.

2-(4-Chlorophenyl)-α-methyl-5-benzoxazoleacetic acid, benoxaprofen (**1**), is a potent inhibitor of carrageenan-induced edema in rats[1] and is currently undergoing clinical trials as a new nonsteroidal antiinflammatory agent. It has also been reported[2] that α-methyl-2-phenyl-5-benzothiazoleacetic acid (**2**) is active against carrageenan-induced

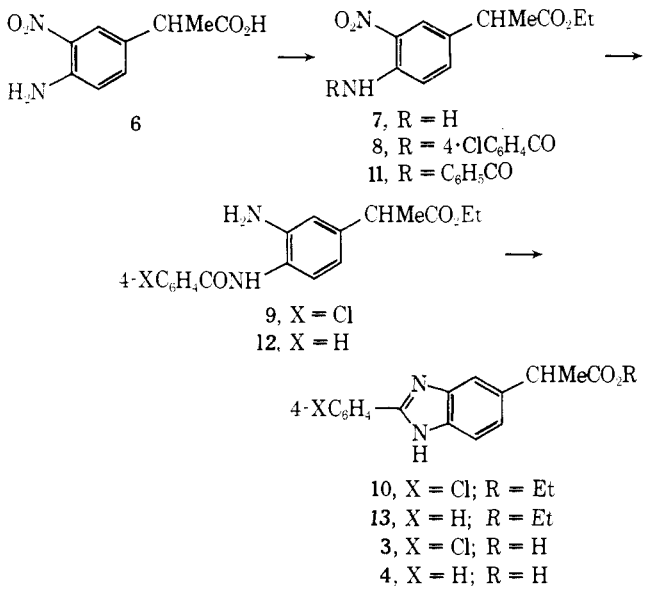


1, X = O; R = Cl
2, X = S; R = H
3, X = NH; R = Cl
4, X = NH; R = H
5, X = NMe; R = Cl

edema. This paper reports the synthesis and carrageenan activity of the benzimidazole isosteres **3** and **4**, the *N*-methyl derivative **5**, and some related compounds.

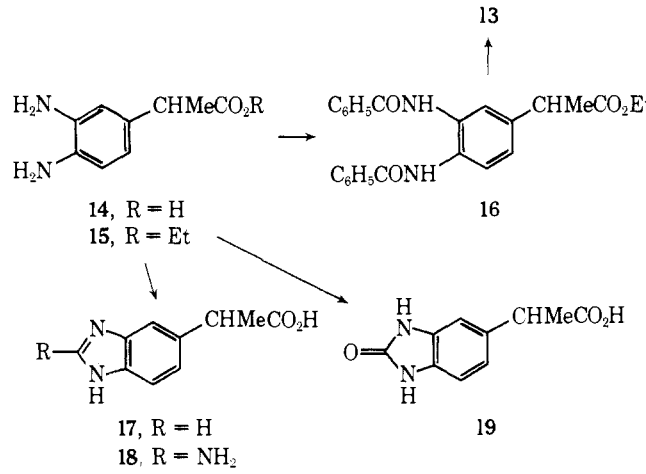
Chemistry. 4-Amino-α-methyl-3-nitrobenzeneacetic acid[3] (**6**) was esterified (Scheme I) under Fischer–Speier conditions, and the ethyl ester **7** was treated with 4-chlorobenzoyl chloride in pyridine. The product **8** was reduced with iron and hydrochloric acid to yield the amino ester **9**. This cyclized smoothly when heated at 220° to give the substituted benzimidazole ester **10** which hydrolyzed to the acid **3** in concentrated hydrochloric acid. The ethyl ester **7** was also treated with benzoyl chloride in pyridine and the product **11** was reduced catalytically to the amino ester **12**. This was converted as before into the substituted benzimidazole ester **13** and the corresponding acid **4**.

Scheme I



The benzimidazole ester **13** was also made from 3,4-diamino-α-methylbenzeneacetic acid[3] (**14**). Esterification of this acid (Scheme II) gave the ester **15** which was treated with an excess of benzoyl chloride in triethylamine. The resulting dibenzoyl derivative **16** cyclized at 220–240° to give the ester **13** in poor yield.

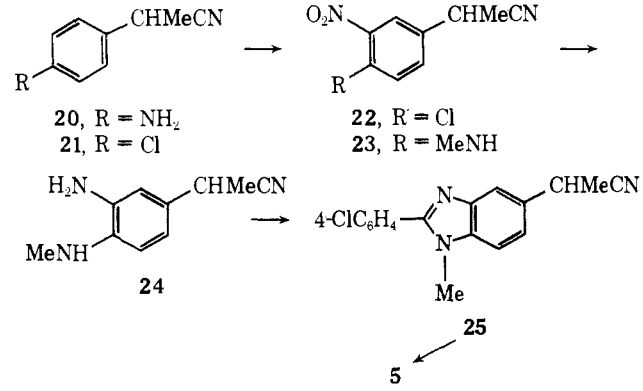
Scheme II



Treatment of the diamino acid **14** with formic acid and with cyanogen bromide gave the parent α-methyl-5-benzimidazoleacetic acid **17** and the 2-aminobenzimidazole **18**, respectively. The reaction of **14** with phosgene gave the 2-benzimidazolone **19**.

Attempts to N-methylate the benzimidazole ester **10** with methyl iodide and dimethyl sulfate were not very successful and were abandoned in favor of the following synthesis of the *N*-methyl derivative **5** (Scheme III). 4-Amino-α-methylbenzeneacetonitrile[4] (**20**) was diazotized and treated with cuprous chloride in hydrochloric acid to give the chloro derivative **21**. This, on treatment with fuming nitric acid at −5°, gave the chloronitro compound **22**. The chlorine atom was then displaced by methylamine to give **23** by heating the reagents at 150° in ethanol. The nitro derivative **23** was subsequently reduced catalytically to give the diamine **24** and this gave the *N*-methylbenzimidazole derivative **25** by condensation with 4-chlorobenzaldehyde and oxidation of the crude product with lead tetraacetate.

Scheme III



The nitrile **25** was finally hydrolyzed to the corresponding acid **5** with refluxing hydrochloric acid.

Biological Results and Discussion. Acids **3–5** and **17–19** were screened for antiinflammatory activity on the carrageenan-induced edema test in rats.[1] Oral doses of 100 mg/kg of **3, 4, 17, 18,** and **19,** and 50 mg/kg of **5,** were given to Wistar rats 3 hr and 0.5 hr before an injection of carrageenan and the amount of inflammation produced during the following 2.5 hr was compared with that produced in a control group of rats dosed with saline. None of the compounds caused a significant reduction in the amount of edema produced. When phenylbutazone and hydrocortizone were tested concurrently at 50 mg/kg, these gave 44–69 and 42–51% reduction, respectively.

The biological activity of molecules is dependent on their molecular shape and other physicochemical characteristics. Since the shapes of the benzimidazoles **3** and **4** are approximately the same as those of the isosteres **1** and **2,** the inactivity of the former compared with the activity of the latter on the carrageenan test must be explained in terms of differences in the other physicochemical properties. In an attempt to define some of these properties, we examined the partition coefficients (see Table I) of compounds **1–4** at physiological pH and concluded that the differences in activity could not be explained in terms of this parameter. On the other hand, the benzimidazoles are clearly more basic than the benzothiazoles and benzoxazoles and this could result in major differences in the interactions between the compounds and biological systems. In addition, the low solubility of compounds **3** and **4** could contribute to their inactivity.

Table I. Partition Coefficients (P) of Compounds 1–4 between 1-Octanol and Phosphate Buffer at pH 7.4

Compd no.	P
1	24.1
2	14.3
3	16.6
4	2.6

Experimental Section

Elemental analyses were carried out by Mr. G. Maciak, Eli Lilly & Co., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values. The NMR spectra were recorded on a Varian A-60A spectrometer.

All of the analyzed compounds, except **22,** are new.

Ethyl 4-Amino-α-methyl-3-nitrobenzeneacetate (7). A warm suspension of 4-amino-α-methyl-3-nitrobenzeneacetic acid[3] (**6,** 21 g, 0.1 mol) in EtOH (400 ml) was saturated with HCl gas and the mixture was heated under reflux for 17 hr. The solvent was evaporated and the residue was equilibrated between Et_2O (200 ml) and 2 *N* NaOH (200 ml). The Et_2O solution was washed with water (3 × 50 ml), dried (Na_2SO_4), and evaporated to yield **7** as yellow crystals (19.5 g, 82%): mp 62–63°. Anal. ($C_{11}H_{14}N_2O_4$) C, H, N. The crystals were recrystallized from EtOH without change of melting point.

Ethyl 4-(4-Chlorobenzoylamino)-α-methyl-3-nitrobenzeneacetate (8). 4-Chlorobenzoyl chloride (7.12 g, 0.041 mol) was added slowly to a stirred solution of **7** (9.7 g, 0.041 mol) in anhydrous pyridine (50 ml) and the solution was heated under reflux for 1.5 hr. The solvent was evaporated and the residue was equilibrated between $CHCl_3$ (100 ml) and 1 *N* HCl (100 ml). The organic layer was washed with H_2O (4 × 50 ml), dried (Na_2SO_4), and evaporated. The residue was recrystallized from EtOH to give **8** as yellow crystals (12.7 g, 83%): mp 93–95°. Anal. ($C_{18}H_{17}ClN_2O_5$) C, H, N.

Ethyl 3-Amino-4-(4-chlorobenzoylamino)-α-methylbenzeneacetate (9). A mixture of **8** (7.15 g, 0.019 mol), reduced Fe powder (11.3 g), concentrated HCl (0.35 ml), H_2O (18.8 ml), and EtOH (75 ml) was heated under reflux for 3 hr and filtered. The filtrate was concentrated to a small volume, diluted with H_2O (200 ml), and basified with 5 *N* NaOH. The solution was extracted with Et_2O (3 × 150 ml) and the organic extracts were washed with H_2O (2 × 100 ml). The Et_2O solution was evaporated and the residue was recrystallized from EtOH–H_2O. This gave **9** as cream crystals (4.7 g, 71%): mp 122–124°. Anal. ($C_{18}H_{19}ClN_2O_3$) C, H, N.

2-(4-Chlorophenyl)-α-methyl-5-benzimidazoleacetic Acid (3). Compound **9** (4.6 g, 0.013 mol) was heated at 220° under N_2 for 30 min. The sample solidified on cooling to give ester **10** (4.4 g, 100%) of >95% purity (TLC).

A solution of KOH (1.0 g, 0.018 mol) in H_2O (2.5 ml) was added to a solution of this ester (2.1 g, 0.0063 mol) in EtOH (40 ml). After 6.5 hr at room temperature, most of the EtOH was removed under reduced pressure at 40° and H_2O (50 ml) was added. The pH was adjusted to 6 by the addition of HCl. The precipitated solid was filtered off and recrystallized from DMF–EtOH. This gave **3** as cream crystals (1.1 g, 57%): mp 293–295° dec; NMR [$(CD_3)_2SO$] δ 1.43 (d, 3 H), 3.73 (q, 1 H), 7.6 (m, 7 H). Anal. ($C_{16}H_{13}ClN_2O_2$) C, H, N. Solubility in water at 25° is less than 0.02 mg/ml.

Ethyl 3-Amino-4-benzoylamino-α-methylbenzeneacetate (12). Ethyl 4-(4-benzoylamino)-α-methyl-3-nitrobenzeneacetate (**11**) was prepared in a similar way to that of compound **8.** Amine **7** (4.76 g, 0.02 mol) gave **11** (6.0 g, 100%) as a yellow viscous gum which could not be induced to crystallize.

The gum (6.0 g, 0.0175 mol) in EtOH (100 ml) was hydrogenated at 60 psi in a Parr apparatus over 10% Pd/C (100 mg). The filtered solution was evaporated and the residue was recrystallized from $CHCl_3$–CCl_4 to yield **12** as white crystals (4.0 g, 73%): mp 118–120°. Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

α-Methyl-2-phenyl-5-benzimidazoleacetic Acid (4). (i) Ethyl α-methyl-2-phenyl-5-benzimidazoleacetate (**13**) was prepared in a similar way to that of compound **10.** Ester **12** (2.5 g, 0.008 mol) gave **13** (2.35 g, 100%) as a viscous gum which refused to crystallize.

(ii) The dibenzoyl ester **16** (1.0 g, 0.0024 mol) was heated at 220° for 1.5 hr and 240° for 3.5 hr under N_2. The product was chromatographed on silica gel (30–120 mesh) (80% Et_2O–20% $CHCl_3$ as eluent) to yield some pure **13** (100 mg, 14%), identical with that obtained in method (i).

Ester **13** (1.1 g, 0.0037 mol) was hydrolyzed in the same way as ester **10** to give cream crystals which were recrystallized from EtOH–H_2O. This gave acid **4** (0.7 g, 66%) as crystals which changed appearance at 106–110° and melted with decomposition at 160–180°. Anal. ($C_{16}H_{14}N_2O_2 \cdot 0.5C_2H_5OH$) C, H, N. Solubility in H_2O at 25° is less than 0.02 mg/ml. The EtOH of crystallization was not removed when the crystals were dried at 60° in vacuo.

Ethyl 3,4-Dibenzoylamino-α-methylbenzeneacetic Acid (16). 3,4-Diamino-α-methylphenylacetic acid (**14**)[3] was esterified to give the corresponding ester **15**[3] as an oil which was not distilled.

Benzoyl chloride (8.6 g, 0.061 mol) was added to a stirred solution of ester **15** (6.3 g, 0.030 mol) in Et_3N (80 ml) and the mixture was stirred under reflux for 4 hr. The solvent was evaporated under reduced pressure and the residue was stirred with 1 *N* HCl (100 ml). The insoluble solid was filtered off, washed with H_2O, and recrystallized from EtOH to give **16** as white crystals (6.8 g, 54%): mp 160–162°. Anal. ($C_{25}H_{24}N_2O_4$) C, H, N.

α-Methyl-5-benzimidazoleacetic Acid (17). A solution of diamine **14**[3] (4.5 g, 0.025 mol) in 98% HCO_2H (15 ml) was heated under reflux for 7 hr under N_2 and evaporated under reduced pressure. The residue was dissolved in H_2O (50 ml) and the pH was adjusted to 6 by the addition of 5 *N* NaOH. A precipitate was formed which was filtered off and recrystallized from EtOH–H_2O. This gave **17** as cream crystals (3.8 g, 80%): mp 260–262°. Anal. ($C_{10}H_{10}N_2O_2$) C, H, N.

2-Amino-α-methyl-5-benzimidazoleacetic Acid (18). A warm stirred solution of diamine **14**[3] (7.75 g, 0.043 mol) in H_2O (300 ml) was cooled to 15° and CNBr (4.55 g, 0.043 mol) was added. A precipitate (probably **14**) formed which dissolved within 3 hr. Later, a different solid was formed. The next day, the pH was adjusted to 6 by the addition of 50% NaOH solution. The solid was filtered off, washed with H_2O, and dried to give **18** as yellow crystals (7.4 g, 84%): mp 308–311° dec. Anal. ($C_{10}H_{11}N_3O_2$) C, H, N.

α-Methyl-2-oxo-2,3-dihydro-5-benzimidazoleacetic Acid (19). $COCl_2$ was bubbled slowly through a solution of diamine **14**[3] (2.5 g, 0.014 mol) in H_2O (20 ml) containing concentrated HCl (2 ml). After 3.5 hr, the solid which had formed was filtered off and recrystallized from EtOH–H_2O. This gave **19** as white crystals (2.05 g, 72%): mp 240–243° (slight decomposition). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

4-Chloro-α-methyl-3-nitrobenzeneacetonitrile (22). 4-Amino-α-methylbenzeneacetonitrile[4] (**20**, 43.8 g, 0.3 mol) was dissolved in a warm solution of concentrated HCl (90 ml) and H_2O (275 ml). The stirred solution was cooled and diazotized at 0–5° by the dropwise addition of a solution of $NaNO_2$ (22.8 g, 0.33 mol) in H_2O (40 ml) during 30 min. After a further 30 min, the diazotized solution was added dropwise during 30 min to a stirred solution of CuCl (30 g, 0.3 mol) in concentrated HCl (100 ml) and H_2O (100 ml) kept at 85–90°. The mixture was stirred at this temperature for a further 30 min, cooled to room temperature, and extracted with Et_2O (3 × 150 ml). The organic solution was shaken with a saturated solution of Na_2CO_3 (100 ml) and H_2O (100 ml), then dried (Na_2SO_4), and evaporated. In this way, chloro compound **21** was obtained as a mobile brown oil (39.0 g, 79%) which was identical with an authentic sample.[2]

The oil (39.0 g, 0.236 mol) was added dropwise during 50 min to a stirred solution of fuming HNO_3 (*d* 1.5, 120 ml) kept at −5–0°. After a further 40 min at this temperature and 2.5 hr at room temperature, the solution was poured onto ice (350 g). The product was extracted with Et_2O (3 × 150 ml) and the extracts were neutralized with a saturated solution of $NaHCO_3$. The Et_2O extracts were finally washed with H_2O (100 ml), dried (Na_2SO_4), and evaporated. This gave pure **22** as a light brown gum (42.0 g, 84%) which solidified on standing: mp 36–39°. Anal. ($C_9H_7ClN_2O_2$) C, H, N.

2-(4-Chlorophenyl)-1,α-dimethyl-5-benzimidazoleacetic Acid (5). 4-Chloro-α-methyl-3-nitrobenzeneacetonitrile[2] (**22**, 19 g, 0.09 mol) was heated and stirred for 5 hr at 150° in a sealed glass vessel with 33% CH_3NH_2 in EtOH and allowed to cool overnight. The mixture was treated with 2 *N* NaOH and extracted with $CHCl_3$ (three times). The combined $CHCl_3$ solutions were dried (Na_2SO_4), filtered, and evaporated to give a product which, after chromatography on silica gel ($CHCl_3$ as eluent), yielded 4-methylamino-α-methyl-3-nitrobenzeneacetonitrile (**23**) as an orange solid (11 g, 60%): NMR ($CDCl_3$) δ 1.63 (d, 3 H), 3.04 (d, 3 H), 3.88 (q, 1 H), 6.93 (d, 1 H), 7.52 (dd, 1 H), 8.1 (m, 1 H), 8.15 (d, 1 H).

The foregoing product (11 g, 0.05 mol) with EtOH (300 ml) and 50% Pd/C (0.5 g) was hydrogenated at room temperature and pressure to give 3-amino-4-methylamino-α-methylbenzeneacetonitrile (**24**, 8.25 g, 88%) as a dark oil which was about 95% pure (TLC). The above nitrile (**24**, 2.6 g, 0.015 mol) and 4-chlorobenzaldehyde (2.12 g, 0.015 mol) were refluxed in C_6H_6 for 0.5 hr, while the theoretical amount (0.26 ml) of H_2O was collected in a Dean-Stark apparatus. The C_6H_6 solution was evaporated to dryness under reduced pressure and the residual oil heated at 100° for 15 min in AcOH (30 ml) containing lead tetraacetate (4.68 g). The brown solution was diluted with H_2O, neutralized with $NaHCO_3$ solution, and extracted with $CHCl_3$. This was dried (Na_2SO_4) and evaporated to dryness and the product was purified by chromatography (SiO_2, $CHCl_3$ eluent) to give 2-(4-chlorophenyl)-1,α-dimethyl-5-benzimidazoleacetonitrile (**25**, 3 g, 69%) as a solid: NMR [$CDCl_3$–$(CD_3)_2SO$] δ 1.09 (d, 3 H), 3.82 (s, 3 H), 4.06 (q, 1 H), 7.32–7.87 (m, 7 H).

The above nitrile **25** (3 g, 0.01 mol) was stirred in refluxing concentrated HCl (30 ml) for 1 hr. The mixture was poured into an excess of $NaHCO_3$ solution and filtered, the pH adjusted to pH 7 with concentrated HCl, and the product extracted with $CHCl_3$ which was dried (Na_2SO_4) and decolorized (C). The $CHCl_3$ was evaporated to yield **5** (1 g, 32%) as a buff solid: mp 225–227°; NMR [$CDCl_3$–$(CD_3)_2SO$] δ 1.54 (d, 3 H), 3.8 (s, 3 H), 3.82 (q, 1 H), 7.25 (m, 7 H). Anal. ($C_{17}H_{15}ClN_2O_2$) C, H, N.

Acknowledgment. We wish to thank our colleagues in the Pharmacology Department of our company for the biological results and Mr. G. L. O. Davies for the partition data. Mr. T. A. Hicks is thanked for supplying details of the preparation of compounds **21** and **22**.

References and Notes

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Analgesics. 3. Selected 1-Substituted and 1,3-Disubstituted 5-Propionoxy-5-(1-phenylethyl)barbituric Acids

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Several 1,3-disubstituted and 1-substituted derivatives of 5-propionoxy-5-(1-phenylethyl)barbituric acid were synthesized and evaluated for analgesic activity. Three of these compounds, 1,3-bis(methoxymethyl)-5-propionoxy-5-(1-phenylethyl)barbituric acid (**2**), 1,3-dimethyl-5-propionoxy-5-(1-phenylethyl)barbituric acid (**7**), and 1-methyl-5-propionoxy-5-(1-phenylethyl)barbituric acid (**10**), exhibited better oral activity than codeine sulfate.

In previous reports[1,2] we have shown that analgesic activity is associated with a series of 5-acyloxy-5-phenylalkylbarbituric acids, and we have discussed the structure–activity relationships of these 5,5-disubstituted compounds. We have now prepared a series of 1,3-disubstituted and 1-substituted derivatives of one of the most potent compounds reported earlier, 5-propionoxy-5-(1-phenylethyl)-barbituric acid, in order to evaluate the effects of nitrogen substituents on the analgesic activity.

Chemistry. 1,3-Bis(alkoxymethyl)-5-propionoxy-5-(1-phenylethyl)barbituric acids (**2–5**) were prepared by alkylation of 5-propionoxy-5-(1-phenylethyl)barbituric acid (**1**) with alkyl chloromethyl ethers in the presence of 2 equiv of base. 1,3-Bis(acetoxymethyl)-5-propionoxy-5-(1-phenylethyl)barbituric acid (**6**) was prepared from **1** and bromomethyl acetate in a similar manner.

1,3-Dialkyl derivatives **7–9** and 1-alkyl derivatives **10** and **11** of 5-propionoxy-5-(1-phenylethyl)barbituric acid were obtained by alkylation of **1** with alkyl halides in the presence of 2 equiv and 1 equiv of base, respectively (Scheme I). No attempts were made to separate any racemates obtained throughout this study.

Structure–Activity Relationships. The best analgesic

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