Synthesis and Antiinflammatory Activity of Some 2-Aryl-6-benzoxazoleacetic Acid Derivatives

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Various approaches to the synthesis of 2-aryl-6-substituted benzoxazoles are described. The products, which included the 6-methyl derivative 4a, ethylamines 10 and 19, ethanols 12 and 14, the acetic and α -methylacetic acids 9 and 16a-f, and the acetic ester 11, were screened for antiinflammatory activity on the carrageenan-induced rat paw edema test. Some of the compounds possessed activity superior to that of phenylbutazone and of the same order as that of benoxaprofen.

Benoxaprofen, 2-(4-chlorophenyl)- α -methyl-5-benzoxazoleacetic acid (1),¹ is a potent new antiinflammatory agent which is currently undergoing clinical trials. This paper describes the preparation of the isomeric α methyl-6-benzoxazoleacetic acid and some related compounds, together with their activity on the carrageenan rat paw edema assay. The syntheses and antiinflammatory activities of a number of other close analogues of benoxaprofen have been published previously.^{1,2}



Chemistry. The synthetic routes to the 2-aryl-6substituted benzoxazole derivatives are illustrated in Schemes I-IV. Complete details are given in the Experimental Section and only points of particular interest will be discussed in this section.

Schemes I and II show the methods which were used to prepare some of the 6-substituted benzoxazole derivatives from 6-amino-3-methylphenol (2). Reaction of this phenol with ethyl benzoate in hot polyphosphoric acid, a reaction which has been used previously to prepare 2-arylbenzoxazoles,³ unexpectedly yielded the novel 6-methyl-2phenyl-5-benzoxazolylphenylmethanone (5) in addition to the normal product 4a. The same mixture of products was obtained when the o-amidophenol 6a was heated in polyphosphoric acid.

Hydrolysis of the benzoxazole ester 13 with concentrated hydrochloric acid at different temperatures yielded different major products. At 100 °C, the main product was the α -methylbenzoxazoleacetic acid 16a while at 160 °C the product was the *o*-aminophenol 17.

More direct approaches to the synthesis of useful building blocks of the type 17 are summarized in Schemes III and IV, together with examples of the conversion of 17 into the 2-aryl- α -methylbenzoxazoleacetic acids 16b-f. Displacement of the halogen of the o-halogenonitrobenzenes 22, 23, 29, and 30 by various oxygen bases was unsuccessful. Decomposition problems possibly associated with the formation of a benzylic anion with 22 were not overcome with 23, 29, and 30 where formation of a benzylic anion would not be possible. Other investigations have previously reported obtaining mixtures and tars in similar displacement reactions with oxygen bases.⁴ A successful direct preparation of 17 was achieved by the nucleophilic displacement of chlorine by the anion of diethyl methylmalonate from 5-chloro-2-nitroanisole (31) to give the o-methoxynitrobenzene 32a. The latter was converted into 17 by the method outlined in Scheme IV.

Antiinflammatory Activity. The antiinflammatory activity of the compounds was assessed in a similar manner to that described previously¹ for the related 2-aryl-5-benzoxazoleacetic acids.

Scheme I. Synthetic Routes to 2-Phenyl-6-benzoxazoleacetic Acid (9) and the Corresponding Ethylamine 10^a



^a Reagents/conditions for method A were PhCOCl + pyridine; B, 200-210 °C; C, p-RCOCl + pyridine; D, pyridine hydrochloride, 200 °C; E, polyphosphoric acid, 200-210 °C; F, PhCO₂Et + polyphosphoric acid, 180-210 °C; G, N-bromosuccinimide; H, NaCN + DMAc; I, 50% H₂SO₄; J, H₂ + Raney Ni + EtOH + NH₃.

The compounds were tested initially on a carrageenan-induced rat paw edema test¹ similar to that described by Winter et al.⁵ Subsequently, representative examples of the active acids were tested on a modified version¹ of the carrageenan test to establish the dose necessary to reduce the foot swelling by 30% (ED₃₀) 2.5 and 5.0 h after the injection of the irritant. When compared with similar data for phenylbutazone and benoxaprofen, the ED₃₀ values gave a measure of the relative potency and duration of action of the compounds.

The activities of the compounds on the initial carrageenan test are summarized in Table I, together with those of hydrocortisone and phenylbutazone, which were tested concurrently. Data for benoxaprofen are also included for comparative purposes.

Compounds 9-12, 14, and 16a-f were active and the 6-methyl derivative 4a and the amine 19 were inactive. The activity of amine 10 in normal rats would appear to be due to adrenal stimulation since the compound was





^a Bx = 2-phenyl-6-substituted benzoxazole. Reagents/ conditions for method A were EtOH + p-MeC₆H₄SO₃H; B, LiAlH₄; C, NaNH₂ + liquid NH₃, MeI; D, NH₃ + glycerol, 150 °C; E, concentrated HCl, 100 °C; F, concentrated HCl, 160 °C; G, POCl₃; H, H₂ + Raney Ni + EtOH + NH₃, then (CH₂CO₂H)₂.





^a Reagents/conditions for method A were 2,4,4,6-tetrabromo-2,5-cyclohexadienone; B, CF₃CO₃H; C, 50% H_2SO_4 ; D, NaOH, NaOAc, NaOMe, or *t*-BuOK in various solvents.

inactive in adrenalectomized animals. In contrast, the acids 9, 16b, and 16d were approximately equiactive in normal and adrenalectomized animals.

Compounds 16b and 16c were selected as representative examples of the active acids of the series and their ED_{30} values were determined. The results are reported in Table II, together with the corresponding figures for benoxaprofen and phenylbutazone. It can be seen that the new compounds compared favorably with the comparator drugs and data not presented in this paper showed that this was also true of their activity against rat adjuvant arthritis.¹⁰

Table II also shows that compounds 16b, 16c, and benoxaprofen were the most effective of the group after 5 h. This is of some significance since compounds with a long duration of action possess obvious advantages in the treatment of chronic diseases such as rheumatoid arthritis.

Experimental Section

Microanalyses were carried out by Mr. G. Maciak, Eli Lilly &

Scheme IV. Alternative Synthetic Route to the Useful Intermediate 17 and the 2-Aryl-a-methyl-6-benzoxazoleacetic Acids 16^a



^a Reagents for method A were $CNaMe(CO_2Et)_2$; B, H₂ + Pd/C; C, 2,4,4,6-tetrabromo-2,5-cyclohexadienone; D, CF₃CO₂H; E, NaOH, NaOAc, NaOMe, or *t*-BuOK in various solvents; F, CNaMe(CO₂Et)₂; G, HBr + HOAc + H₂O; H, EtOH + HCl, then NaOH; I, (a) ArCHO, then Pb(OAc)₄, NaOH + EtOH + H₂O, HCl, or (b) ArCOCl + pyridine, then 220 °C, NaOH + EtOH + H₂O, HCl.

Company, Indianapolis, Ind. Where analyses have been carried out as indicated by the symbols of the elements, the results obtained were within 0.4% of the theoretical values. The melting points are uncorrected. The IR and NMR spectra of all new compounds were consistent with their structures.

2'-N-Benzamido-5'-methylphenyl Benzoate (3). Benzoyl chloride (20 mL, 0.17 mol) was slowly added to a stirred solution of 6-amino-3-methylphenol (10 g, 0.08 mol) in pyridine (100 mL). The solution was then heated on a steam bath for 2 h. The solvent was removed in vacuo and the residue was crystallized from EtOH-H₂O to give 3 (15.7 g, 58%): mp 148-150 °C. Anal. $(C_{21}H_{17}NO_3)$ C, H, N.

2'-Hydroxy-4'-methylbenzanilide (6a). Benzoyl chloride (210 mL, 1.81 mol) was steadily added to a solution of 6-amino-3methylphenol (200 g, 1.60 mol) in pyridine (1400 mL). The temperature was kept at 5 °C throughout the addition and was then allowed to rise to ambient temperature. The solution was heated on a steam bath for 2 h and evaporated to dryness. A small amount was washed with H₂O and crystallized from *i*-PrOH-H₂O to give white crystals of 6a: mp 170 °C. Anal. ($C_{14}H_{13}NO_2$) C, H, N.

4-Chloro-2'-hydroxy-4'-methylbenzanilide (6b). Preparation analogous to 6a using 4-chlorobenzoyl chloride afforded, after crystallization from EtOH, 6b: mp 214 °C. Anal. ($C_{14}H_{12}CINO_2$) C, H, N.

Table I. Biological Activity of the 2-Aryl-6-Substituted Benzoxazoles on the Carrageenan-Induced Rat Paw Edema Test^a



				Antiinflammatory act. vs. carrageenan ^a				
				Test compd		Comparator drug		
No.	\mathbf{R}^1	R²	Approx LD ₅₀ in mice, mg/kg po	Dose, mg/ kg × 2	% inhibn of edema	Compd	$\begin{array}{c} \text{Dose,} \\ \text{mg/} \\ \text{kg} \\ \times 2 \end{array}$	% inhibn of edema
4a	Ph	Me	<1600	50	10 ^b	HC ^c	50	62
9	Ph	CH ₂ CO ₂ H	1200	$100 \\ (100$	60 50) ^d	HC	50	60
10	Ph	$(CH_2)_2 NH_2 \cdot HCl$	300	25 (25	59° 0) ^d	PB ^e	100	62
11	Ph	CH,CO,Et	1200	100	61	PB	100	60
12	Ph	(CĤ,),ÔH	>1600	100	47	HC	50	51
14	Ph	CHMeCH,OH	800	100	61	PB	50	53
16a	Ph	CHMeCO ₂ H	600	50	60	HC	50	51
16b	$2-\text{ClC}_{6}\text{H}_{4}$	CHMeCO ₂ H	1200	50 (50	$\frac{41}{58}^{d}$	PB	50	40
16c	4-ClC ₆ H ₄	CHMeCO,H	1200	50	28	PB	50	39
16d	$2,4-Cl_{2}C_{6}H_{3}$	CHMeCO ₂ H	300	25 (25	49 56) ^d	HC	50	42
16e	$4 - FC_{4}H_{4}$	CHMeCO, H	1200	50	48	HC	50	58
16f	4-MeČ ₆ H₄	CHMeCO ₂ H	1200	50	43	HC	50	42
19	Ph	$CHMeCH_2NH_2 \cdot 0.5(CH_2CO_2H)_2$	300	25	0	HC	50	51
Benoxaprofen			800	50	78	PB	50	61

^a The method described in ref 1 was used. The compounds, in carboxymethylcellulose, were dosed orally 3 and 0.5 h prior to an injection of 0.1 mL of a 1% suspension of carrageenan in 0.9% saline into the plantar surface of the right hind foot of each of four rats. The edema was measured 2.5 h after the carrageenan injection. ^b Result not significant on Student's t test at p > 0.02. ^c Hydrocortisone. ^d Result in rats 5 days after adrenalectomy. ^e Phenylbutazone.

Table II. Carrageenan Test ED_{30} Values^{*a*} for Acids 16b, 16c, Benoxaprofen, and Phenylbutazone

	ED ₃₀ values, mg/kg				
Compd	2.5 h	5 h			
16b 16c Benoxaprofen Phenylbutazone	$\begin{array}{c} 1.98 \pm 3.02 \\ 2.40 \pm 4.35 \\ 13.4 \pm 2.9 \\ 23.8 \pm 12.1 \end{array}$	$\begin{array}{c} 23.04 \pm 7.97 \\ 11.0 \pm 7.79 \\ 10.6 \pm 7.0 \\ 52.6 \pm 7.6 \end{array}$			

^a The method described in ref 1 was used. Three different doses of the compounds, in carboxymethylcellulose, were dosed orally 1 h before an injection of 0.1 mL of a 1% suspension of carrageenan in 0.9% saline into the plantar surface of the right hind foot of each of four rats. The edema was measured at 2.5 and 5 h after the carrageenan injection. $ED_{30} = \text{dose} \pm \text{standard error required to give 30% reduction of foot swelling.}$

6-Methyl-2-phenylbenzoxazole (4a). (i) The impure 2'hydroxy-4'-methylbenzanilide (**6a**)-pyridine hydrochloride mixture was heated at 220 °C for 1 h. The residue was cooled and extracted with Et₂O. The solution was washed successively with 2 N HCl (twice) and 2 N NaOH, dried (Na₂CO₃), treated with C, and evaporated to dryness to give **4a** (315 g, 93% over two stages): mp 93 °C. Anal. (C₁₄H₁₁NO) C, H, N.

(ii) Compound 3 (8.0 g, 0.024 mol) was heated at 200–210 °C for 20 min. The cooled residue was dissolved in CHCl₃ (70 mL), extracted with 2 N NaOH (25 mL), and washed with H_2O (3 × 50 mL). The dried (Na₂SO₄) organic solution was evaporated to yield an off-white solid (4.9 g, 97%), mp 92–93 °C, identical with the previous sample.

2-p-Chlorophenyl-6-methylbenzoxazole (4b). Cyclization of 4-chloro-2'-hydroxy-4'-methylbenzanilide (6b) as described for the formation of 4a gave a solid, 4b (81% over two stages): mp 151 °C. Anal. ($C_{14}H_{10}$ ClNO) C, H, N.

6-Methyl-2-phenyl-5-benzoxazolylphenylmethanone (5). (i) A mixture of 6-amino-3-methylphenol (10 g, 0.08 mol), ethyl benzoate (15 mL, 0.10 mol), and polyphosphoric acid (80 mL) was heated at 180–210 °C for 20 min. The solution was poured onto ice and the resulting emulsion was extracted with Et_2O . The Et_2O solution was washed with H_2O (twice), dried (Na₂CO₃), and evaporated to dryness. GC analysis of the residual oil showed that it was a mixture of 4a and 5. In repeat experiments, the ratio of the two products varied and the variation is thought to be due to the different qualities of polyphosphoric acid which were used. Pure 4a was isolated from the mixture as well as pure 5: mp 121–123 °C. Anal. ($C_{21}H_{18}NO_2$) C, H, N.

(ii) Compound 6a (5.0 g, 0.022 mol) was heated with polyphosphoric acid (100 g) at 200-210 °C for 20 min. The product was again a mixture of 4a and 5.

6-Bromomethyl-2-phenylbenzoxazole (7). A solution of **4a** (50 g, 0.239 mol) in CCl₄ (250 mL) containing *N*-bromosuccinimide (50 g, 0.281 mol) was heated under reflux in the presence of UV light for 3 h. The solution was filtered and allowed to cool. The resulting crystals were recrystallized from CCl₄ to yield **7** (30 g, 46%): mp 163 °C. Anal. ($C_{14}H_{10}BrNO$) C, H, Br, N.

2-Phenyl-6-benzoxazoleacetonitrile (8). A mixture of 7 (15 g, 0.052 mol), NaCN (60 g, 1.22 mol), and dimethylacetamide (300 mL) was stirred at room temperature for 7 h and evaporated under reduced pressure. The residue was extracted with CHCl₃. This filtered solution was washed with H₂O and evaporated to dryness. The solid product was crystallized from EtOAc-Et₂O to give 8 (5.2 g, 43%): mp 145 °C. Anal. ($C_{15}H_{10}N_{2}O$) C, H, N.

2-Phenyl-6-benzoxazoleacetic Acid (9). The nitrile 8 (10 g, 0.042 mol) was dissolved in 50% H_2SO_4 . The solution was heated under reflux for 1.5 h and was poured into ice- H_2O . A solid was produced which was removed by filtration and crystallized from Et₂O-EtOAc to yield 9 (1.2 g, 13%): mp 170 °C. Anal. (C₁₅H₁₁NO₃) C, H, N.

2-Phenyl-6-benzoxazoleethylamine Hydrochloride (10). A solution of 8 (8.9 g, 0.038 mol) in EtOH (300 mL) saturated with NH₃ was hydrogenated over Raney nickel W2 catalyst (250 mg, 0.003 mol) at room temperature at 60 psi for 24 h. The solution was filtered and evaporated to dryness. The residue was dissolved in 2 M HCl and the solution was washed with CHCl₃. The aqueous solution was evaporated to a small volume when crystallization occurred. This yielded 10 (2.2 g, 21%): mp 268 °C. Anal. ($C_{15}H_{14}ClN_2O$) C, H, N.

Ethyl 2-Phenyl-6-benzoxazoleacetate (11). A solution of 9 (150 g, 0.593 mol) and *p*-toluenesulfonic acid (500 mg, 0.003 mol) in C_6H_6 (1400 mL)-EtOH (600 mL) was heated under reflux for 24 h and the C_6H_6 -EtOH- H_2O azeotrope was removed. The

residue, after removal of solvent, was dissolved in $CHCl_3$ and this solution was washed with 2 N NaOH, dried (Na_2CO_3) , and evaporated. This yielded 11 (166 g, 99%): mp 76 °C. Anal. $(C_{17}H_{15}NO_3)$ C, H, N.

2-Phenyl-6-ben zoxazoleethanol (12). Ester 11 (20 g, 0.071 mol) was slowly added to a solution of LiAlH₄ (3.0 g, 0.079 mol) in dry Et₂O (200 mL). The resulting mixture was heated at 100 °C for 3 h and poured carefully into ice (1 kg)-concentrated HCl (100 mL). The Et₂O layer was separated and the H₂O layer was extracted with Et₂O (twice). The extracts were combined and dried (Na₂SO₄) and the solvent was removed in vacuo. The residue was crystallized from EtOH-H₂O to give 12 (12 g, 71%): mp 89 °C. Anal. (C₁₅H₁₃NO₂) C, H, N.

Ethyl α -Methyl-2-phenyl-6-benzoxazoleacetate (13). A suspension of 11 (8 g, 0.028 mol) in dry Et₂O (50 mL) was added to a solution of sodamide (from Na, 750 mg, 0.033 mol) in liquid NH₃ (120 mL). The red solution was stirred for 10 min. A solution of MeI (2.0 mL, 0.049 mol) in Et₂O (10 mL) was added as rapidly as possible. After the vigorous exothermic reaction, the solution was stirred for 1 min; then NH₄Cl (2 g, 0.038 mol) was added and the solvent was evaporated. The residue was extracted with Et₂O. The filtered solution was treated with C and evaporated to dryness to give 13 (8.1 g, 97%): mp 46 °C. Anal. (C₁₈H₁₇NO₃) C, H, N.

 β -Methyl-2-phenyl-6-benzoxazoleethanol (14). LiAlH₄ (0.8 g, 0.021 mol) was added to a stirred solution of 13 (8.7 g, 0.029 mol) in dry Et₂O (50 mL). The mixture was stirred for 1 h at room temperature and poured carefully into ice (500 g)-concentrated HCl (50 mL). The Et₂O layer was separated and the H₂O layer was extracted twice with Et₂O. The extracts were combined and washed with 2 N NaOH and then H₂O. The solution was dried (Na₂CO₃) and the solvent was removed in vacuo. The residue was crystallized from EtOH-H₂O to give 14 (2.1 g, 28%): mp 98 °C. Anal. (C₁₆H₁₅NO₂) C, H, N.

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 α -Methyl-2-phenyl-6-benzoxazoleacetamide (15). A suspension of 13 (27 g, 0.092 mol) in saturated NH₃-glycerol (100 mL) was heated in a bomb at 150 °C for 24 h. The mixture was then diluted with ice-H₂O (150 mL). The solid was removed by filtration and crystallized from EtOH-DMF to give 15 (20 g, 82%): mp 193 °C. Anal. (C₁₆H₁₄N₂O₂) C, H, N.

Diethyl 3-Methoxy- α -methyl-4-nitrophenylmalonate (32a). A solution of diethyl methylmalonate (110 g, 0.63 mol) in dry DMF (100 mL) was steadily added to a stirred suspension of NaH (14.5 g, 0.61 mol) in dry DMF (100 mL) as the temperature was kept <20 °C by external cooling. After the addition, the mixture was stirred for 2 h. A solution of 5-chloro-2-nitroanisole⁶ (100 g, 0.53 mol) in dry DMF (100 mL) was added and the solution was stirred at 100 °C for 24 h. The solution was evaporated to dryness and the residue was dissolved in Et₂O. This solution was washed with H₂O (three times) and evaporated to dryness. Vacuum distillation of the residue afforded pure **32a** (50.9 g, 29%): bp 170–174 °C (0.1 mm). Anal. (C₁₅H₁₉NO₇) C, H, N.

3-Hydroxy- α -methyl-4-nitrobenzeneacetic Acid (33). A solution of 32a (70.5 g, 0.22 mol) in 49% HBr-H₂O (500 mL) and 33% HBr-AcOH (300 mL) was heated under reflux for 9 h. The solution was filtered and evaporated to dryness. The residue was dissolved in an aqueous solution of NaHCO₃. This solution was washed with CHCl₃, treated with C, and acidified (pH 1) with concentrated HCl. The mixture was extracted with CHCl₃ and the organic solution was treated with C, filtered, dried (Na₂SO₄), and evaporated to dryness. The residue was crystallized from toluene-petroleum ether (bp 80–100 °C) to give 33 (34.4 g, 75%): mp 95–97 °C. Anal. (C₃H₉NO₅) C, H, N.

4-Amino-3-hydroxy- α -methylbenzeneacetic Acid (17). (i) A solution of 33 (1 g, 0.005 mol) in EtOH (10 mL)-H₂O (5 mL) containing 10% Pd/C (100 mg) was hydrogenated at 60 psi for 3 h at ambient temperature. The mixture was filtered and the filtrate was evaporated to dryness. The residue was crystallized from H_2O -AcOH to give 17 (700 mg, 82%): 169–170 °C. Anal. (C₉ $H_{11}NO_3$) C, H, N.

(ii) A solution of 13 (10 g, 0.034 mol) in concentrated HCl (150 mL) was heated in a bomb at 160 °C for 24 h and evaporated to dryness. The residue was dissolved in H₂O and this solution was washed with CHCl₃ and evaporated to dryness to give the hydrochloride of 17 (5 g, 68%): mp 197–199 °C. This, on neutralization with aqueous NH₄OH, gave pure 17, identical with the previous sample.

Ethyl 4-Amino-3-hydroxy- α -methylbenzeneacetate (34). A solution of the hydrochloride of 17 (4.9 g, 0.023 mol) in saturated EtOH-HCl (100 mL) was heated under reflux for 6 h and evaporated to dryness. The residue was dissolved in H₂O and the solution was neutralized (pH 7) with 2 N NaOH. The product was continuously extracted with CHCl₃ and organic solution was washed once with H₂O. Evaporation of the solvent afforded 34 (2.5 g, 52%): mp 114-115 °C. Anal. (C₁₁H₁₅NO₃) C, H, N.

 α -Methyl-2-phenyl-6-benzoxazoleacetic Acid (16a). A solution of impure 13 (15 g, 0.051 mol) in concentrated HCl (150 mL) was heated on a steam bath for 6 h and poured into ice-H₂O. The solid which was produced was filtered off and dried. The solid was dissolved in CHCl₃ and chromatographed on a SiO₂ column. Evaporation of the eluent afforded 16a (7.8 g, 57%): mp 132 °C. Anal. (C₁₆H₁₃NO₃) C, H, N.

2-(2-Chlorophenyl)-α-methyl-6-benzoxazoleacetic Acid (16b). A solution of 2-chlorobenzaldehyde (4.3 g, 0.031 mol) and 34 (6 g, 0.029 mol) in toluene (100 mL) was heated under reflux and the H₂O which formed was removed using a Dean-Stark apparatus. The solvent was removed in vacuo and the residue was dissolved in AcOH (100 mL). This solution was treated with Pb(OAc)₄ (15 g, 0.034 mol) below 25 °C. The solution was kept overnight and poured into ice- H_2O . The resulting mixture was extracted with Et₂O (200 mL). The organic solution was washed with H₂O and 2 N NaOH, dried (Na₂CO₃), and evaporated to give slightly impure ethyl 2-(2-chlorophenyl)- α -methyl-6-benzoxazoleacetate (6.6 g, 70%). This was dissolved in EtOH (20 mL) and treated with a solution of NaOH (1.5 g, 0.038 mol) in $\mathrm{H_{2}O}$ (10 mL). After being stirred for 0.5 h, further H_2O (20 mL) was added. After 1.5 h, the solution was evaporated to dryness in vacuo. The residue was dissolved in H₂O and the solution was washed with CH_2Cl_2 . The solution was acidified (pH 3) with concentrated HCl and extracted with CH₂Cl₂. The extract was dried (Na_2SO_4) and treated with C, and the solvent was removed in vacuo. The residual oil was crystallized from Et₂O to give 16b (2 g, 33%): mp 108-110 °C. Anal. (C₁₆H₁₂ClNO₃) C, H, Cl, N.

2-(4-Chlorophenyl)- α -methyl-6-benzoxazoleacetic Acid (16c). Compound 34 was treated with 4-chlorobenzoyl chloride in the same manner as in the preparation of 6a and the product was cyclized by method (i) for 4a. The slightly impure ethyl ester of 16c was hydrolyzed by the procedure used for 16a. The product was crystallized from H₂O-acetone to give pure 16c (1.4 g, 10% over three stages): mp 195–196 °C. Anal. (C₁₆H₁₂ClNO₃) C, H, Cl, N.

2-(2,4-Dichlorophenyl)- α -methyl-6-benzoxazoleacetic Acid (16d). Compound 34 was condensed with 2,4-dichlorobenzaldehyde and the product was cyclized and hydrolyzed under the conditions described for 16b to give, after crystallization from toluene-petroleum ether (bp 80–100 °C), pure 16d (24% over three stages): mp 143–145 °C. Anal. (C₁₆H₁₁Cl₂NO₃) C, H, Cl, N.

2-(4-Fluorophenyl)- α -methyl-6-benzoxazoleacetic Acid (16e). This compound was prepared from 34 and 4-fluorobenzoyl chloride by a method similar to that described for 16c, except that the hydrolysis was as described for 16b. Recrystallization from EtOH-H₂O gave pure 16e (54% over three stages): mp 147 °C. Anal. (C₁₆H₁₂FNO₃) C, H, F, N.

 α -Methyl-2-(4-methylphenyl)-6-benzoxazoleacetic Acid (16f). This compound was prepared from 34 and 4-methylbenzoyl chloride by the method described for 16c, but the hydrolysis was as described for 16b. Recrystallization from EtOH-H₂O afforded pure 16f (46% over three stages): mp 167-168 °C. Anal. (C₁₇H₁₅NO₃) C, H, N.

 α -Methyl-2-phenyl-6-benzoxazoleacetonitrile (18). A solution of 15 (9 g, 0.034 mol) in POCl₃ (100 mL) was heated under reflux for 2 h and then the solvent was removed in vacuo. Ice (20 g) was added to the residual oil and the mixture was extracted

with CHCl₃. The organic solution was dried (Na₂CO₃) and evaporated to dryness to give 18 (8.2 g, 98%): mp 121 °C. Anal. ($C_{16}H_{12}N_2O$) C, H, N.

 β -Methyl-2-phenyl-6-benzoxazoleethylamine Hemisuccinate (19). Compound 18 was reduced as described for 10a and the hemisuccinate derivative was prepared. This was crystallized from EtOH-DMF to give pure 19 (4.9 g, 39%): mp 205 °C. Anal. (C₁₈H₁₉N₂O₃) C, H, N.

4-Amino-3-bromo- α -methylbenzeneacetonitrile (21). 2,4,4,6-Tetrabromo-2,5-cyclohexadienone⁷ (103 g, 0.31 mol) was slowly added to a stirred solution of 4-aminophenyl- α -methylacetonitrile⁸ (20) (36.5 g, 0.25 mol) in CH₂Cl₂ (650 mL) at -30 °C. When the addition was complete the mixture was stirred for a further 1 h at -20 °C. When the solution reached ambient temperature, it was washed with cold 2 N NaOH, dried (Na₂CO₃), and evaporated to give 21 (51.5 g, 92%) as an oil: NMR (aryl) δ 6.65 (d, 5-H), 7.00 (dd, 6-H), 7.29 (d, 2-H). Anal. (C₃H₃BrN₂) C, H, Br, N.

3-Bromo- α -methyl-4-nitrobenzeneacetonitrile (22). Trifluoroacetic anhydride (78 mL) was added to a stirred suspension of 90% H₂O₂ (12.3 mL, 0.3 mol) in CH₂Cl₂ (300 mL) at 0 °C, and the stirred mixture was cooled in Drykold-acetone. After 5 min, a solution of **21** (22.5 g, 0.1 mol) in CH₂Cl₂ (30 mL) was slowly added so that gentle reflux conditions were maintained. The solution was then heated under reflux for 1 h, cooled, and washed with ice-H₂O and an aqueous solution of Na₂CO₃. The dried (Na₂CO₃) solution was evaporated to give **22** (24 g, 94%) as a yellow oil: NMR (aryl) δ 7.55 (dd, 6-H), 7.79 (d, 2-H), 7.90 (d, 5-H). Anal. (C₉H₇BrN₂O₂) C, H, Br, N.

Diethyl 4-Amino- α -methylphenylmalonate (27). The reaction of 4-fluoronitrobenzene (25) with the anion of diethyl methylmalonate was carried out as described for the preparation of 32a. Impure 26 was isolated as an oil (about 80% pure by NMR analysis). A solution of this material in EtOH (100 mL) containing 10% Pd/C (1 g) was hydrogenated at 60 psi for 4 h at room temperature. The solution was filtered and the solvent was removed in vacuo. The residual oil was distilled in vacuo to yield the amine 27 (88.3 g, 32% over two stages), bp 156-161 °C (0.3 mm), as a yellow oil. The amine was characterized as its acetyl derivative in the following way. Acetyl chloride (3.87 g) was added to a stirred mixture of some of the amine (13.05 g) and KHCO₃ (4.95 g) in toluene (50 mL). The mixture was stirred under reflux for 1.5 h and filtered. Evaporation of the filtrate gave an oil which solidified on standing. This was pure diethyl 4-acetylamino- α -methylphenylmalonate (14.8 g, 98%): mp 74-75 °C. Anal. $(C_{16}H_{21}NO_5)$ C, H, N.

Diethyl 3-Bromo- α -methyl-4-nitrophenylmalonate (29).

2,4,4,6-Tetrabromo-2,5-cyclohexadienone⁷ (31 g, 0.094 mol) was slowly added to a stirred solution of **27** (20 g, 0.08 mol) in CH₂Cl₂ (300 mL) at room temperature. After being stirred for 2 h, the solution was washed with 2 N NaOH and H₂O, dried (Na₂CO₃), and evaporated to give slightly impure **28** (22.6 g, 86%). A solution of this product (3 g) in CH₂Cl₂ (3 mL) was added in one portion to a stirred solution of 30% H₂O₂ (8 mL), 0.2 mol) in trifluoracetic anhydride (55 mL). The solution was stirred for 3 h, washed with H₂O and 2 N NaOH, dried (Na₂CO₃), and evaporated to dryness to give **29** as an oil (2.2 g, 68%): NMR (aryl) δ 7.48 (dd, 6-H), 7.77 (d, 2-H), 7.83 (d, 5-H). Anal. (C₁₄H₁₆BrNO₆) C, H, Br, N.

Attempted Preparation of Compounds 24 and 32. Attempted displacements of halogen from compounds 22, 23 (slightly impure by NMR analysis, prepared from 22 by hydrolysis as for 9), 29, and 30^9 were unsuccessful under the following conditions: (i) reaction of the compounds with hot or cold solutions of NaOH in H₂O and also in the presence of DMF; (ii) with NaOAc in AcOH and H₂O; (iii) with NaOMe and NaOEt in MeOH, EtOH, Me₂SO, and HMPT at various temperatures and concentrations; (iv) with KO-t-Bu in t-BuOH.

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3,4-Methylenedioxyphenyl-, Isopropylidenedioxyphenyl-, and Benzyl-Substituted Chiral 2-Aminosuccinimides and 3-Aminopyrrolidines. Stereoselective Investigations of Potential Anti-Parkinsonian, Antipsychotic, and Anticonvulsant Activities¹

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The chiral title compounds 2–11 were assessed for their potential anti-Parkinsonian, antipsychotic, and anticonvulsant properties. The most striking differences in the biological activity of enantiomeric pairs were noted for D-(R)-2-amino-N-(3,4-methylenedioxyphenyl)succinimide hydrochloride (2) vs. L-(S)-3 and D-(R)-2-amino-N-(3,4-iso-propylidenedioxyphenyl)succinimide (4) vs. L-(S)-5. D-(R)-2 partially attenuated amphetamine-induced stereotyped behavior, whereas D-(R)-4 antagonized oxotremorine-induced tremors. Their respective enantiomorphs were inactive in these tests. No differences in anticonvulsant potency of enantiomeric pairs were observed. The stereoselective actions of D-(R)-2 and 4 were rationalized on the basis of the presence or absence of gem-dimethyl functions in isopropylidenedioxy scenes, the data seem to indicate that these methyl groups influence selective receptor site interaction in the D-(R) series.

Piribedil (1), like apomorphine, is thought to act by direct stimulation of central dopaminergic receptors but

possesses a more prolonged duration of action.^{2,3} Whereas this compound exhibits anti-Parkinsonian activity, it is less